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Original Communications

CARDIAC MANIFESTATIONS IN FRIEDREICH'S ATAXIA

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ALTHOUGH Friedreich's ataxia is considered to be an uncommon neurological disorder, we have encountered five patients with this condition within the last eighteen months, three of whom presented cardiac manifestations. In addition, a patient encountered during 1947 at the London Hospital, Whitechapel, is included in this report. Although it is well known that electrocardiographic abnormalities occur in this condition, our interest was stimulated by the first case seen at Victoria Hospital, London, Ontario, in that the presenting problem was that of cardiac failure occurring in an undiagnosed case of paralysis in a young man. Soon after admission it became apparent that the neurological disorder was Friedreich's ataxia. Having encountered a similar case during 1947 in which the cardiac aspect had become the patient's major disability, our attention was directed to a further study of the cardiac manifestations in this neurological disorder.

Friedreich's ataxia is generally regarded as affecting only the central nervous system. A review of the literature, however, reveals that the heart may be often affected and in particular the electrocardiogram may be disturbed. Newton Pitt[6] in 1887 described heart failure as the outstanding feature of the last phases of a case of Friedreich's ataxia. French workers have taken more interest in its cardiac aspect than American or British physicians, with the result that the published case records of Friedreich's disease contained little with regard to the heart until the paper by Evans[2] in 1942, reviewing thirty-eight cases, twelve of which revealed electrocardiographic abnormalities. From Evans' work it is apparent that the electrocardiogram may help to establish the diagnosis of Friedreich's ataxia. When the neurological manifestations are not typical of the condition, an abnormal tracing gives support to the diagnosis, but a normal curve does not exclude it. In three of our cases we considered the electrocardiographic findings to be of value in establishing the diagnosis. In two of

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our cases the electrocardiogram was normal and in both the diagnosis was not classical in that these patients showed increased knee jerks with little involvement except in the legs. Nevertheless, they have been included because of the familial nature and since the diagnosis was made by a neurologist.

Although Friedreich in 1861 and 1863 described a familial ataxic disorder which he declared to be a "new disease," the syndrome was not accepted until 1882 when "hereditary ataxia" was considered as an entity and the term Freidreich's disease was proposed. There appear to be no racial, geographical, or social factors related to the disease. The primary cause appears to be an inherited abnormality, but nothing is known, however, as to what might damage the germinal material resulting in defective germinal mutation by which the condition originates.

The condition usually appears before the age of puberty, although late cases do occur. Consequently, the chance of inheritance beyond a single generation is slight; hence the majority of cases are "familial." Friedreich's ataxia might be considered as the most common of the hereditary or familial ataxias. The literature contains many descriptions of related disorders and it is convenient to apply "hereditary or familial ataxia" to this group. The group is characterized pathologically by degenerations of some or all of the optic nerves, the cerebellum, the olives, and the long ascending and descending tracts of the spinal cord. Although the typical case of Friedreich's disease stands alone, the signs and symptoms may vary considerably depending on anatomical locations of the degenerative process. It is generally felt that each variety tends to breed true but this is not invariably so, for there are a number of reports in which more than one form has occurred in the same family. It would appear that these transitional forms are due to the same underlying abnormality affecting different portions of the central nervous system.

In Friedreich's disease the degeneration is most marked in the lateral and posterior columns, especially the tract of Goll. It is usually most intense in the lower cord but may involve the medulla and bulb, and in these cases cardiac arrhythmia (without cardiac lesion), vomiting, sweating, polyuria, glycosuria, hyperthermia, disordered breathing, etc. are considered by some to be the result of disturbance to the vagus nerve and its bulbar connections (Russell[8]). The lateral columns are also involved, especially the pyramidal tracts and the dorsal spinocerebellar tracts, together with the cells of Clarke's column. The spinal cord is usually small and may be greatly reduced in size. The cerebrum and cerebellum are usually normal but may show some atrophy. Histologically the degenerated parenchyma is replaced by an intense whorl-like glial overgrowth. The heart may show changes similar to those seen in the central nervous system. Russell[8] described a chronic interstitial myocarditis in four patients with Friedreich's ataxia, three of whom showed marked cardiac hypertrophy. In these cases there was no histological evidence of damage in the region of the vagal nuclei. Microscopically there was a focal destruction of muscle fibers with fibrosis and hypertrophy of the surviving fibers. There was a random distribution of fatty degeneration of the muscle fibers. The fibers were widely

separated by a uniform increase of delicate collagenous tissue in which a moderate number of spindle fibroblasts were present. There was an uneven scanty infiltration with small lymphocytes and fewer eosinophils and neutrophilic leucocytes. The purkinje fibers of the node and conducting system were similarly separated by fibrous tissue and a sparse cellular infiltration. Russell feels that this myocarditis is of toxic origin and, in view of the association with Friedreich's ataxia and pathological similarities, that the same agent is responsible for both cardiac and neurological lesions.

There are accounts of families showing both the Friedreich's and Marie syndromes (spastic ataxia) and also of the intermediate forms (Roth,[7] Wilson[4]). Spillane[9] reported a family showing peroneal muscular atrophy, Friedreich's disease, and an abortive amyotrophic disorder. Roth[7] reported two families, one showing two siblings with Charcot-Marie-Tooth and abortive Friedreich's, and in the other family two examples of Friedreich's associated with four examples of heart disease in six siblings.

Since this report deals primarily with the cardiac manifestations of Friedreich's disease, a review of the clinical course and neurological aspects is not included. Four of the six cases to be described are typical of the Friedreich's syndrome and in these cases the heart was found to be affected also. The remaining two cases might be considered as variants of Friedreich's disease or early manifestations of the disorder, in view of the presence of exaggerated deep reflexes and the general clinical pattern. These two patients present no cardiac abnormalities up to the present time. The diagnosis was confirmed by a neurologist in all cases.

CASE REPORTS

CASE 1.—C. P., a 24-year-old man, was admitted to Victoria Hospital, London, Ontario, June 9, 1948, in a condition of acute heart failure. The patient was apparently well until the age of 14 years, at which time he injured his back in a fall from a bicycle. Following hospital treatment some difficulty in walking was first noted. In 1942 at another hospital a myelogram was done, followed by operation the lower cervical spine. At this time a very small atrophic cord was found. The difficulty in walking increased until a definite staggering gait developed and this lack of control spread to involve the arms, trunk, and neck. Some seven to eight years after the first symptoms, he was confined to a hospital for incurables. Approximately eight months prior to admission, exertional dyspnea, in addition to a marked degree of ataxia, was noted, climaxed by the acute episode which led to the patient's admission. Little of the past history was obtained other than that he was apparently well until 14 years of age, having had measles, whooping cough, and chicken pox prior to 8 years of age. The patient's father died suddenly at an early age from "heart disease." A paternal uncle had also died of heart disease. As far as could be learned, no other member of the family suffered a similar complaint.

Examination showed a slender, somewhat stuperous young man with marked respiratory distress, orthopnea, distended neck veins, a rapid, irregular heart rate of 140, a marked pulse deficit, and a blood pressure of 90/60 mm. Hg. There was no peripheral edema and the chest was clear on auscultation. Clinically the rapid, irregular cardiac rhythm appeared to be auricular fibrillation. The heart was enlarged clinically and confirmed by x-ray, showing a general but predominately left-sided enlargement. Cardiac murmurs where present but difficult to asses in the presence of the rapid, irregular rate. There was a harsh systolic murmur in the mitral area, together with a mid-diastolic gallop rhythm and an inconstant early diastolic murmur. The electrocardiogram revealed right axis deviation, multiple auricular and ventricular extrasystoles producing the rapid, irregular rhythm. (Fig. 1.)

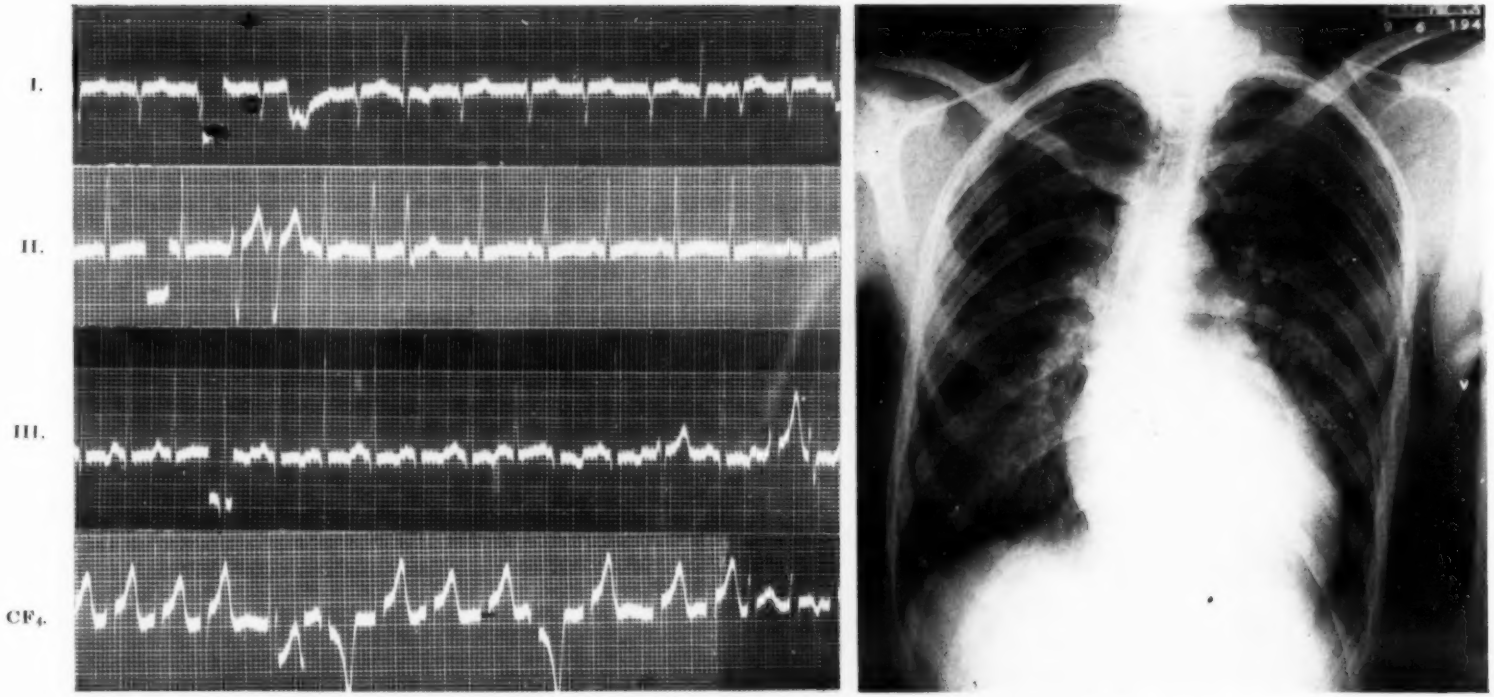

Fig. 1.—Case 1, C. P. Electrocardiogram (Leads I, II, III, and CF_4) and x-ray appearance on admission, June 9, 1948. Note multiple auricular and ventricular extrasystoles, with runs of auricular tachycardia, acute congestive failure.

The neurological examination revaled an obvious cerebellar ataxia with decreased tone, absent reflexes, and gross ataxia in the arms. There was a definite degree of titubation of the head, scanning speech defect, and slight nystagmus. Scoliosis, pes cavus, bilateral extensor plantar responses with absent knee and ankle jerks were present. The legs were somewhat spastic with an equinovarus pes cavus foot deformity and were grossly ataxic.

An attempt was made to control the cardiac emergency in this case with quinidine. The following day little or no improvement had occurred. The patient had become more drowsy, was neauseated with vomiting, and showed increased venous engorgement. The heart remained irregular, and there was a harsh systolic mitral murmur. Gallop rhythm persisted with a loud pulmonary second sound. The possibility of an associated mitral stenosis was considered. The patient was digitalized with marked improvement. The sixth day following admission dyspnea

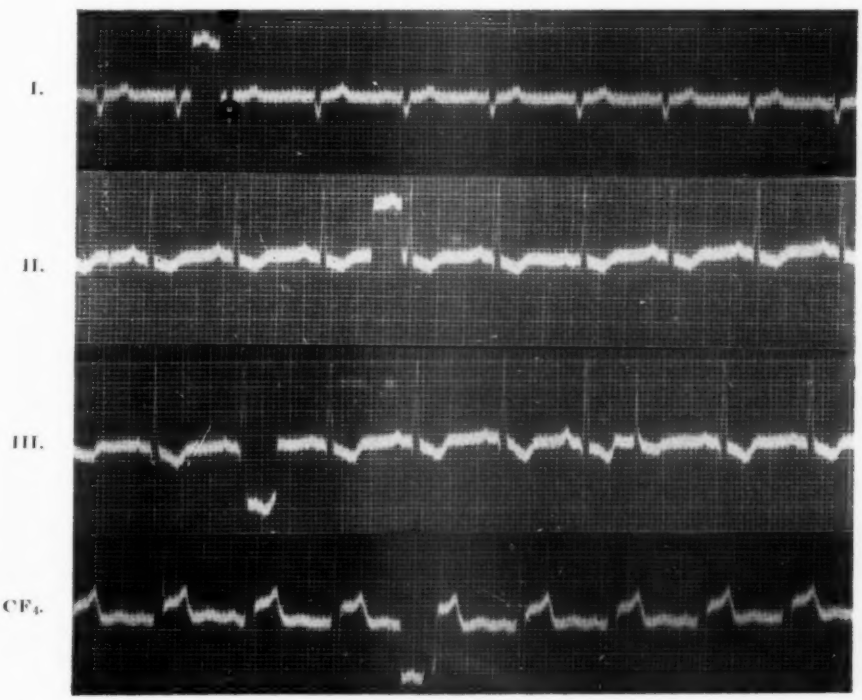

Fig. 2.—Case 1, C. P. Electrocardiogram (Leads I, II, III, and CF_4) taken nine days after admission following control of congestive failure with digitalis. Note sinus rhythm, rapid rate, occasional extrasystoles, right axis deviation.

had decreased, the heart rate was slower but still somewhat irregular, and the signs of congestive failure were definitely subsiding. (Fig. 2.) By the eleventh hospital day the patient was considerably improved, auscultation now revealed a mitral systolic murmur only, and this was not harsh nor as loud as noted previously. Congestive failure was well controlled, following digitalization, on a daily dose of 1½ grains. A moderately rapid sinus rhythm was present with occasional extrasystoles. The ectopic beats decreased in number until discharge, when moderately rapid sinus rhythm was present, with, however, the T-wave configuration of a posterior cardiac infarct which remained unaltered (Fig. 3) during the last three weeks in the hospital. The x-ray examination of the heart on admission revealed an obvious cardiac enlargement with some hilar congestion, which did not appear unlike that of mitral stenosis. Following control of the rapid ectopic rhythm and congestive failure, there was a decrease in cardiac size with no radiological evidence of mitral stenosis. A final chest plate gave similar findings, showing a definite left-sided enlargement and

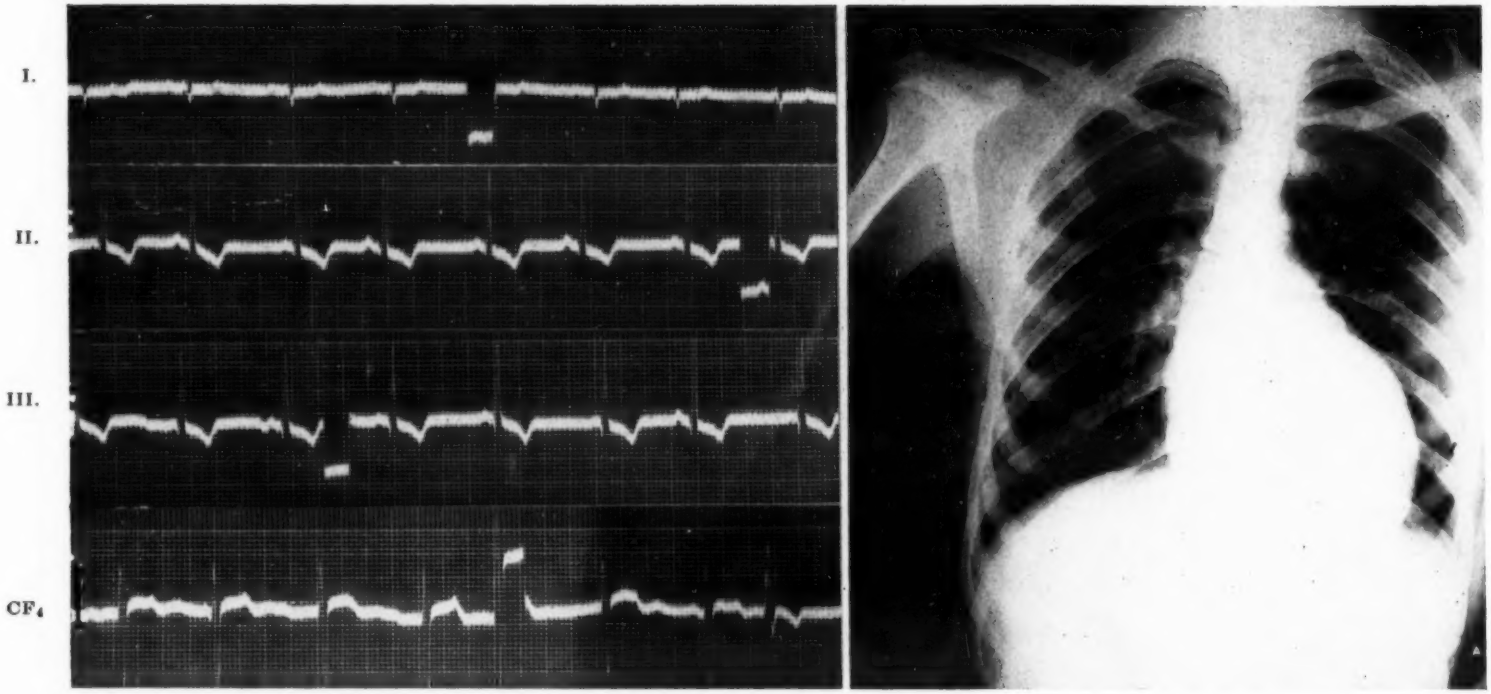

Fig. 3.—Case 1, C. P. Electrocardiogram (Leads I, II, III, and CF_4) and x-ray appearance on discharge from the hospital July 3, 1948. Note sinus rhythm, wandering pacemaker, occasional extrasystoles, right axis deviation, T_2 and T_3 deep negative waves similar to posterior infarction.

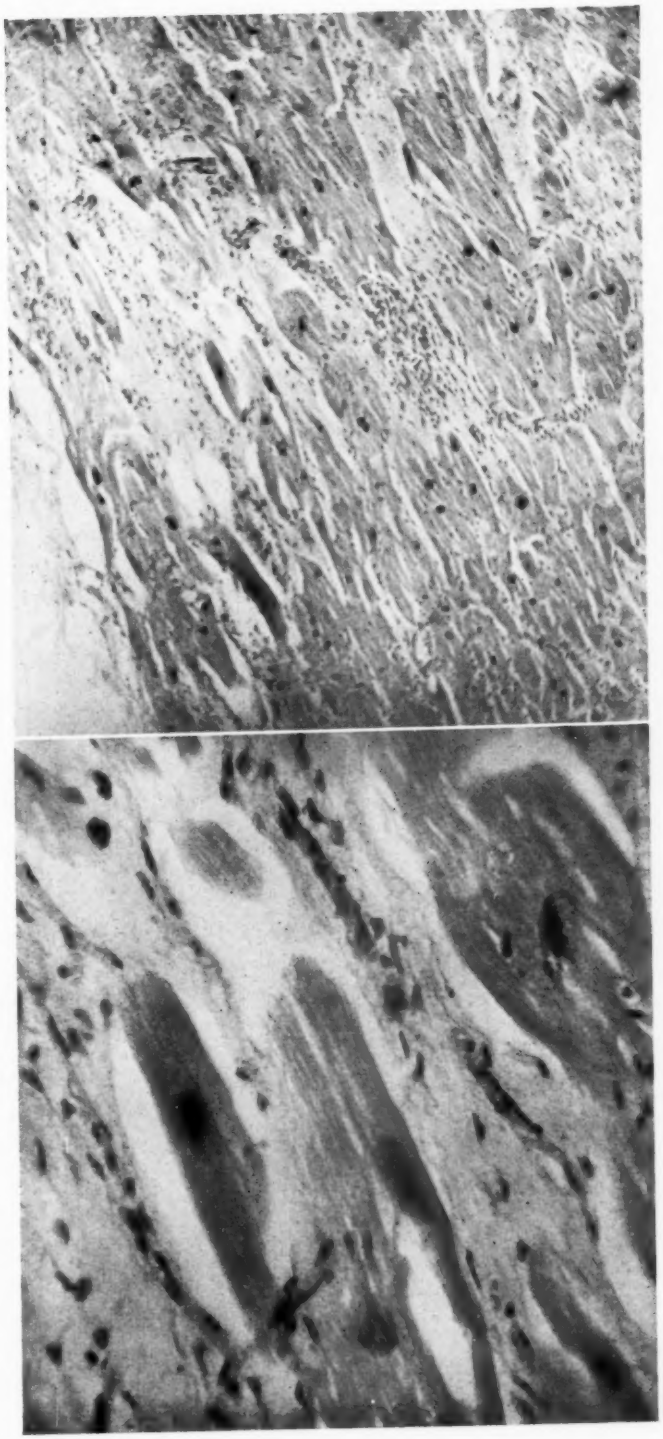

Fig. 4.—Case 1, C. P. Photomicrographs of the heart (high power on the left, low power on the right) showing diffuse fibrosis with scanty cellular infiltration, separation of myocardial fibers and hypertrophy of remaining fibers.

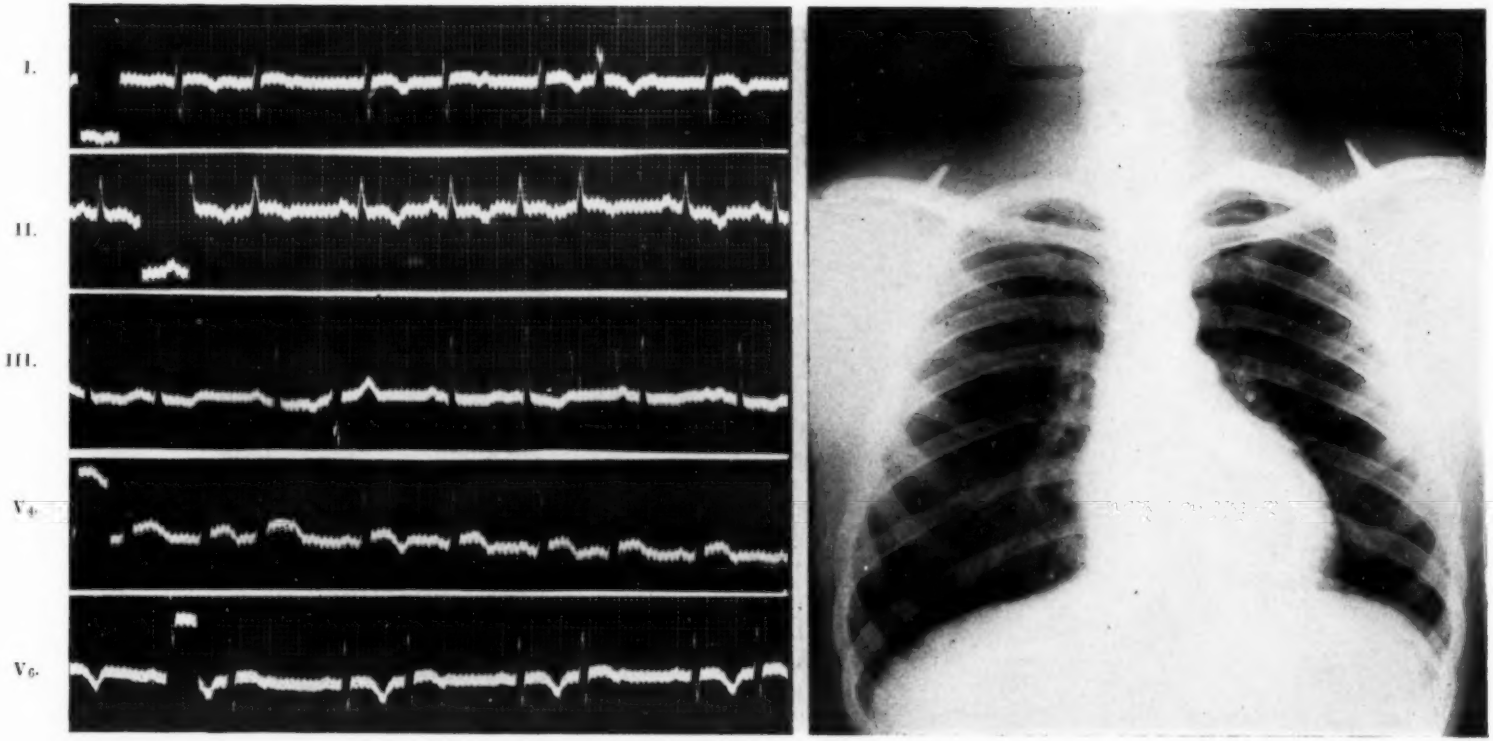

Fig. 5.—Case 2, R. W., July 5, 1949. Electrocardiogram (Leads I, II, III, V_4, and V_6) and x-ray appearance during hospitalization. Note rapid, irregular rhythm, frequent auricular and ventricular extrasystoles. Right axis deviation and negative T waves in Leads I, II, III, V_4, and V_6 are similar to those seen in cardiac infarction.

small aorta. (Fig. 3.) The patient was discharged to home care on digitalis, grains 1½ per day, without failure and with sinus rhythm. He was confined to a wheelchair due to his primary disorder of Friedreich's ataxia. The patient apparently continued well at home from the cardiac standpoint for a few months. However, a further episode of congestive failure did occur, for the follow-up revealed that the patient died of congestive failure Dec. 17, 1948. The clinical diagnosis in this case was confirmed at post mortem Dec. 17, 1948. The heart weighed 705 Gm. There were no significant valvular lesions, no endocardial vegetations, and the coronary arteries appeared normal. There was a diffuse fibrosis, with spindle fibroblasts and a scanty lymphocytic infiltration replacing and separating the myocardial fibers with hypertrophy of the remaining fibers. (Fig. 4.)

CASE 2.—R. W., a 22-year-old man, was admitted to Victoria Hospital April 12, 1949, complaining of calf pain, difficulty in walking and in speaking, and some palpitation. He was apparently well until the age of 16 years, when he first noted some difficulty in walking associated with a "fatigued" or "tired" feeling in the legs. The staggering gait became progressively more disturbing and was associated with loss of balance, particularly on bending over.

In the previous eighteen months the patient and relatives had noted a steady progression in an uncontrollable sway in walking, nodding head movements, awkward arm movements, "disorganized eye movements," and slow, difficult speech. In addition, the patient complained of increasing calf pains in the year prior to admission and shortly before admission he had been disturbed by an irregular heart action which he felt was not constant. He complained also of occasional dyspnea unrelated to exertion. The patient had received a course of liver injections one year prior to admission. One sibling (Case 3) was also affected.

On examination the patient appeared to be a well-developed young man with staring gaze, slow, scanning speech, titubation of the head, a dissociation of conjugate deviation on rapid gaze to the right, some lateral nystagmus, and a fine rotary nystagmus. The palpebral fissures were widened. A mild dorsal scoliosis and pes cavus were present. There was a definite weakness in the legs, most marked peripherally, with no evidence of spasticity. The deep reflexes were absent in both arms and legs with bilateral extensor plantar responses. There was diminished superficial sensation over the lower extremities and vibration sense was intact with definite impairment of position sense in the toes. There was an obvious cerebellar type of ataxia most marked in the lower extremities but quite evident in the trunk muscles, neck, and arms. The electrocardiograms showed a rapid sinus rhythm of 110, right axis deviation with frequent auricular and ventricular extrasystoles, and low to negative T waves in the limb and precordial leads (Fig. 5) somewhat similar to the findings of posterior infarction. His blood pressure was 122/88 mm. Hg. Treatment in the hospital consisted of physiotherapy and ephedrine, which, the patient felt, gave some relief to calf pain. The electrocardiogram remained the same throughout his stay in the hospital. X-ray examination revealed some degree of left ventricular enlargement.

CASE 3.—S. W., a 23-year-old male patient (brother of Case 2) was admitted to Victoria Hospital on June 13 for investigation of a progressive paralysis beginning two years after an attack of poliomyelitis at the age of 11 years which involved the left leg and required a splint for support. The patient was able to get around fairly well until aged 19 years, when weakness, which at that time involved the right leg also, staggering gait, and occasional falling necessitated the use of crutches. The symptoms progressed until about two years prior to admission, when it became impossible for the patient to walk at all, and by this time a definite incoordination in the arms was noted. There was no history of cardiac symptoms in this case.

Examination revealed a slight dissociation of conjugate eye movements with no definite lateral nystagmus; however, some rotary nystagmus was present. All movements were poorly coordinated with some degree of cerebellar ataxia in the arms which was particularly evident in the performance of rapid alternating movement. Some ataxia of the trunk and neck muscles was present. A similar type of incoordinated ataxia was noted in the lower extremities. There was obvious wasting and weakness of both legs, especially marked on the left side. A left foot drop and right pes cavus with scoliosis of the upper thoracic spine to the right was present. The deep reflexes were present and equal in the arms. The abdominal reflexes were absent in all quadrants. In the legs the deep reflexes were completely absent with a marked right extensor plantar response

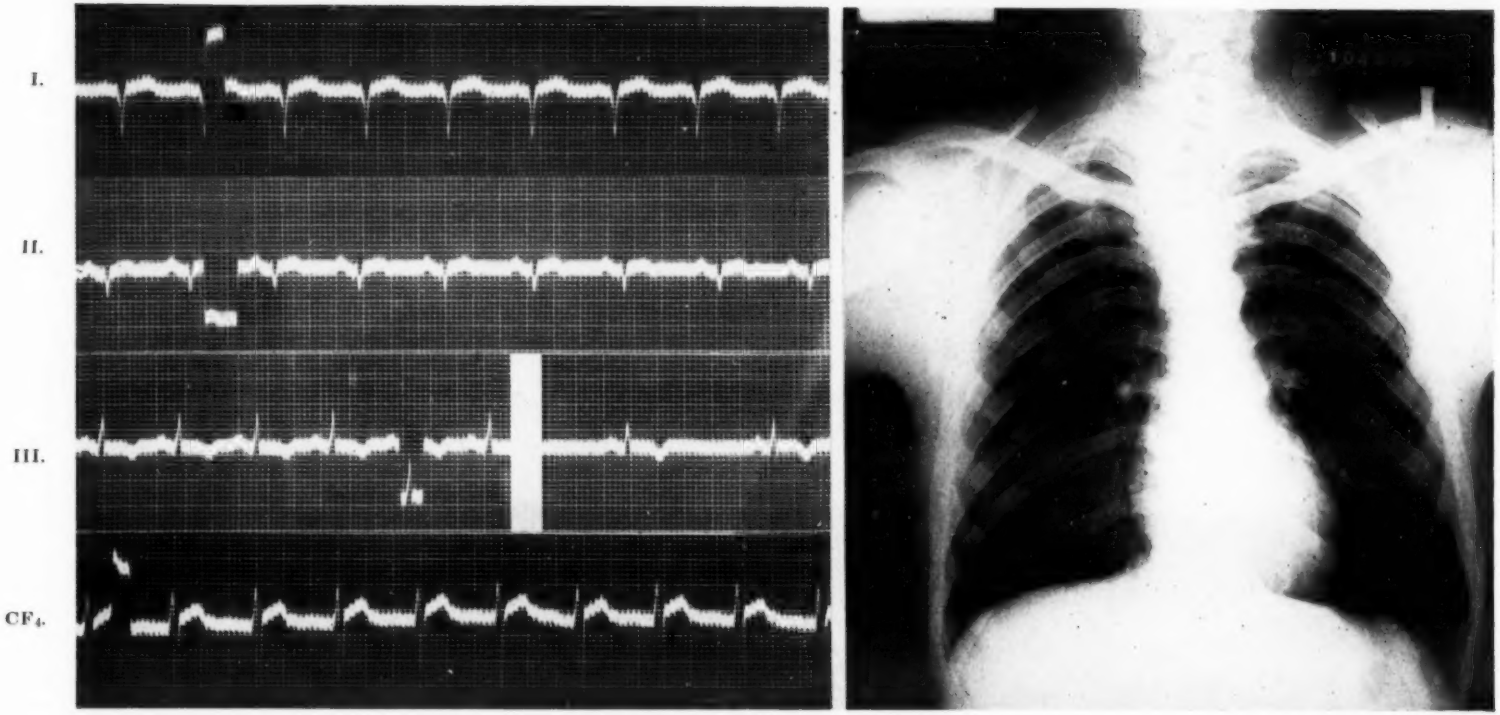

Fig. 6.—Case 3, S. W., July 8, 1949. Electrocardiogram (Leads I, II, III, and CF_4) and x-ray appearance during hospitalization. Note rapid sinus rhythm, marked right axis deviation with QS_1, low diphasic T_2, negative T_3 increased in negativity by deep inspiration.

and a left flexor response. Vibration sense was diminished over the lower extremities and the sense of position was absent in the great toes. No abnormalities were detected on cardiac examination other than the electrocardiographic findings, which showed a marked right axis deviation, slightly negative T_2 and negative T_3. The precordial leads showed a somewhat elevated S-T segment in CF_4 and negative T in CF_6 and CF_7, findings similar to those noted in the patient's brother (Case 2) and suggestive of posterior infarction. The blood pressure was 130/80 mm. Hg with a heart rate of 80 to 100, usually a rapid sinus rhythm. The heart was not enlarged on x-ray examination and the lung fields were clear. (Fig. 6.)

CASE 4.—R. D., a 32-year-old man, was admitted to London Hospital, Whitechapel, Nov. 17, 1946, with a known diagnosis of Friedreich's ataxia since the age of 14 years, complaining of short attacks of vertigo, tinnitus, and weakness associated with a rapid heart rate and dyspnea, increasing in frequency and severity during the previous two years.

This patient, whose symptoms were first observed at about the age of 13 years, presented the classical signs and symptoms of Friedreich's ataxia. There was a marked degree of ataxia and incoordination. The peculiar "mouse-like" titubation of the head was obvious, together with marked ataxia of the trunk, arms, and legs and a definite scanning speech defect. The deep reflexes were absent in both arms and legs with definite bilateral extensor plantar responses. There was loss of position sense in both fingers and toes. Bilateral pes cavus and scoliosis were present. The electrocardiogram had shown obvious abnormalities since at least 27 years of age, and these consisted of a deep, negative T_1 and negative T_2, a deep negative T wave in CR_4, findings similar to those seen in anterior infarction (1941 record). At this time there were no cardiovascular signs or symptoms and the rhythm was regular. Paroxysmal tachycardia was first noted at the age of 29 years. The frequency of these attacks increased until treatment of the cardiac disorder became necessary. In the hospital, these attacks were found to be due to paroxysmal tachycardia. The electrocardiogram on admission (Fig. 7) showed frequent extrasystoles and bouts of tachycardia, in addition to the T-wave changes previously noted. The attacks were considerably diminished in frequency and duration by quinidine. The electrocardiogram at the time of discharge showed a regular sinus rhythm with the T-wave changes resembling posterior infarction. The patient was discharged from the hospital considerably improved except with regard to the primary neurological disorder, to continue on treatment with quinidine. (Fig. 7.)

CASE 5.—G. K., a 16-year-old girl (sister of Case 6), was admitted to the hospital Aug. 14, 1948, for investigation of a peculiar stumbling, swaying gait since the age of 13 years. The patient first complained of a stiffness in the left hip resulting in some difficulty in walking, and stumbling. The difficulty in walking became pregressively worse during the next three years until admission, at which time she had a spastic, stumbling gait.

The parents are first counsins; there are nine siblings, six of whom appeared to be well. One brother (Case 6) suffers from a similar disorder; another brother (never in the hospital) presents a similar, but milder picture. The patient's mother is said to suffer from high blood pressure and "dizzy spells." The maternal grandfather has had paraplegia for ten years. The paternal grandfather died of "heart disease."

The patient was a stubborn, uncooperative, mentally deficient girl, who showed on examination little of significance except with regard to the neurological system. Cardiovascular examination revealed a normal sized heart. Chest x-rays were not done. The rhythm was irregular with a heart rate of 88; the blood pressure was 126/72 mm. Hg. There were no murmurs present and the second sound was reduplicated. The irregularity noted clinically was found to be due to a fairly well-marked degree of sinus arrhythmia by electrocardiogram, which showed also a minor degree of right axis deviation, bilateral extensor plantar responses with a mild pes cavus, and a Harrison sulcus chest deformity. The gait was considered to be a mildly spastic scissors type with considerable stumbling in all directions. There was no evidence of hypotonia. Vibration and position sense were considered to be normal. The neurological opinion in view of the stumbling gait (even though it appeared somewhat spastic), familial features, and nystagmus, was that of early Friedreich's ataxia.

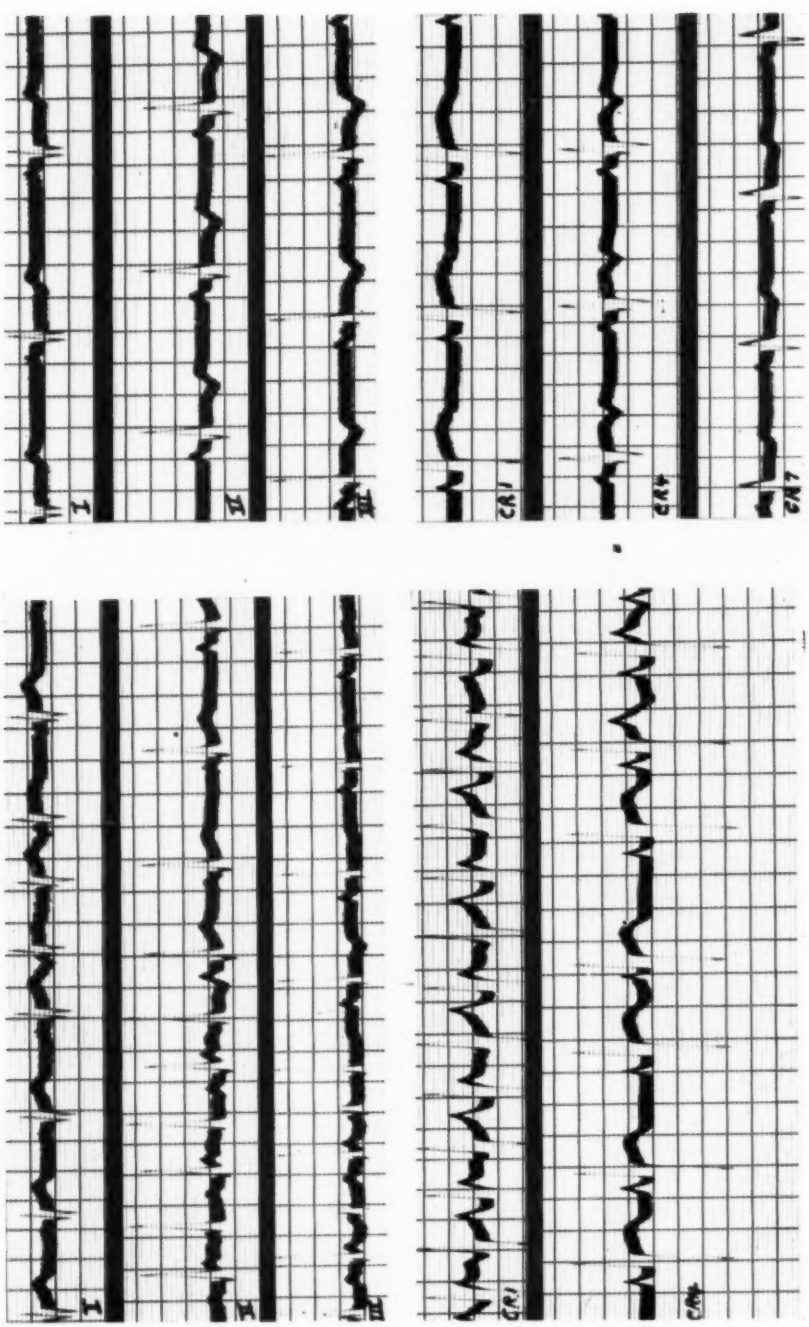

Fig. 7.—Case 4. R. D. *Left*, electrocardiogram, appearance on admission (Leads I, II, III, CR_1, and CR_4). Note rapid, irregular rhythm, multiple auricular extrasystoles, and paroxysms of tachycardia.

Right, electrocardiogram showing sinus rhythm following treatment with quinidine (Leads I, II, III, CR_1, and CR_7) T wave is negative in Leads II, III, CR_4, and CR_7, changes similar to those seen in cardiac infarction.

CASE 6.—B. K., a 13-year-old boy (brother of Case 5), was admitted to Victoria Hospital on Aug. 4, 1948, for investigation and possible treatment of difficulty in walking. When he was 11 years old, his parents observed that his gait was clumsy, appeared weak, and that he swung his legs to the side in walking. Both of his sides appeared equally affected. The parents felt that there had been little or no progression of this difficulty. The patient's sister (Case 5) is similarly affected.

The patient was a somewhat undernourished, quiet boy, who was considered to be of dull-normal intelligence. Abnormal physical findings were confined to the neurological system. The cardiovascular examination was normal, the blood pressure 130/80 mm. Hg, heart rate 80 with regular sinus Rhythm, and the electrocardiogram was normal in all respects. Lateral, vertical, and rotary nystagmus (all fine) were noted by different observers on different occasions. There was no evidence of titubation of the head, intention tremor, or ataxia in the arms. Muscle tone and power appeared normal. The deep reflexes were present and equal in the arms and hyperactive in the legs with classical bilateral extensor plantar responses. A minor degree of unsustained bilateral ankle clonus was present. Motor power in the legs appeared normal. There was some spacticity, the gait was considered to be slightly spastic, and in walking a "scissors" type of gait was apparent with high stepping. Vibration sense was intact with a questionable impairment of position sense. A dorsal scoliosis and mild pes cavus were present.

This patient (and his sister, Case 5) present the picture of a spastic paraplegia with little evidence of cerebellar dysfunction. However, the neurological opinion, in view of the nystagmus, familial features, awkward stumbling gait, mild pes cavus, and scoliosis, was that this is early Friedreich's ataxia.

In Cases 5 and 6 there was no cardiac disorder and the electrocardiogram was considered to be normal (although right axis deviation and marked sinus arrhythmia were present in Case 5). Furthermore, these cases are most likely variants of the typical Friedreich's syndrome, although they certainly appear to be examples of the familial heredo-ataxic group. The cerebellar dysfunction, however, was slight, and the cardiac disorder frequently seen in the more typical Friedreich's case was absent. The absence of deep reflexes in the first four cases again appears to parallel the incidence of cardiac changes.

DISCUSSION

The frequent occurrence of cardiac changes in Friedreich's disease (30 per cent) and the association between abnormal cardiographic changes and the family history suggest the inheritance of a lethal gene which affects both the heart and the central nervous system. The familial nature of the disease is apparent in five of the six cases reported in this communication. A cardiac disorder was the patient's major complaint in two cases and in two others obvious electrocardiographic abnormalities were present. It is of interest to note that the four cases with cardiac manifestations were also the obvious Friedreich's ataxia cases. The remaining two cases, although they were considered to be early Friedreich's ataxia, showed exaggerated deep reflexes and perhaps represent a varient of the syndrome. Evans and Wright,[2] in a study of thirty-eight cases of Friedreich's ataxia, have shown a significant association between family history, speech defect, absent deep reflexes with extensor plantar responses, and the occurrence of electrocardiographic abnormalities. Our cases agree with these findings in that the four patients with cardiac manifestations showed similar signs. In Evans series the rhythm was normal in all except one case, in which the rate was slow from heart block and somewhat irregular from ventricular extrasystoles. In our cases, three of the four showing cardiac effects presented an irregularity in rhythm, and in two of these the patient was hospitalized because of the cardiac disorder. Case 1 recovered from cardiac failure on treatment with digitalis

TABLE I. CLINICAL FEATURES

Cases	1	2	3	4	5	6
Age	24	22	23	32	16	13
Chief complaint	Palpitation and extreme dyspnea	Calf pain; ataxia; palpitation	Weakness; ataxia	Palpitation; faintness and vertigo; dyspnea	Stumbling spastic gait	Stumbling spastic gait
Ataxia	+	+	+	+	Some	Some
Speech defect	+	+	Slight	+	No	No
Nystagmus	Slight	+	Slight	− ?	Slight	Slight
Reflexes						
Biceps	−	−	+	+	++	−
Knee	−	−	−	−		
Plantar	↗	↗	↗↙	↗	↗	↗
Pes cavus	+	+	+	+	Slight	Slight
Scoliosis	+	Slight	+	+	Slight	+
Cardiac signs and symptoms	Rapid irregular rhythm; acute H. F.; transient murmurs, etc.	Rapid rate; multiple extrasystoles; no H. F.	None	Paroxysmal tachycardia; collapse; dyspnea	None	None
X-ray of chest	L. V. + Hil. C.	L. V. +	Heart normal	?	?	?
ECG findings	R. A. D.; rapid, irregular rate; frequent A and V. extrasystoles; later E. C. G. of Post. C. I. with N. R.	R. A. D.; tachycardia with frequent A. and V. extrasystoles; flat to negative T waves (T_2, T_3, Cf_4)	R. A. D.; T-wave changes	Paroxysmal tachycardia and later negative T_2, T_3, TCR_4, TCR_7	Marked S. A.; minor R. A. D.	Normal

H.F.=heart failure.
L.V.=left ventricle.
Hil. C.=hilar congestion.
R.A.D.=right axis deviation.
A. & V.=auricular and ventricular.
C.I.=cardiac infarction.
N.R.=normal rhythm.
S.A.=sinus arrhythmia.

but has since died in congestive failure. Irregularity of the heart's action in Friedreich's ataxia has been noted from time to time in French literature and has been ascribed to bulbar sclerosis involving the vagal nuclei and therefore facilitating sympathetic overactivity. Russell, however, could not confirm this. In the British and American literature there appears to be little or no reference to irregular heart action. Four of our patients showed T-wave abnormalities resembling cardiac infarction when the abnormal rhythm was controlled. The most common finding in Evans and Wright's series also was that of obvious T-wave changes similar to those seen in anterior or posterior infarction. It would appear likely that the pathological changes known to occur in the myocardium have, in those cases with a T_1, or T_3 type of curve, involved predominantly anterior or posterior portions of the heart comparable to the areas involved when the right or left coronary artery is occluded. From the pathological findings in the heart (Russell[8]) and the work of Laubry and deBalsac,[5] who, on radio-opaque injection of the coronaries of the heart in a case of Friedreich's ataxia, found no abnormalities, it would appear that a disturbance of coronary circulation is not responsible for the myocardial degeneration found post mortem. It is not likely that the patients with Friedreich's ataxia in which the electrocardiogram is normal may in time develop heart disease. As it would appear from the cases reported here, the presence of electrocardiographic abnormalities suggests the eventual onset of heart failure, and furthermore in these cases this was associated initially with a rapid, irregular heart action due to multiple auricular and ventricular extrasystoles and bouts of tachycardia. Left ventricular enlargement occurred in 25 per cent of the Evans series and in three of the four cases reported by Russell,[8] and has been reported from time to time in the earlier literature. Cardiac signs and symptoms can occur in the absence of left ventricular enlargement, as in two of the cases reported here, particularly when these are due to a rapid, irregular heart action and paroxysmal tachycardia. The addition of cardiac enlargement, however, certainly darkens the outlook and heralds the onset of further or progressive cardiac failure. It was apparent, however, that treatment is effective in preventing progression, at least for a time, by restoring a more normal rhythm.

Recently Evans[3] has described "familial cardiomegaly" which he has shown in five of ten cases to be familial. Clinically the condition is characterized initially by insignificant symptoms and is often discovered fortuitously in young adults during a routine examination. In these cases giddiness, Stokes-Adams attacks, or sudden death may occur as the result of heart failure precipitated by the onset of paroxysmal tachycardia. The electrocardiogram shows obvious abnormalities, including extrasystoles, paroxysmal tachycardia, auricular fibrillation, heart block, and T-wave abnormalities. The heart is enlarged by the time significant symptoms develop. The prognosis depends on the degree of cardiac enlargement. Pathologically the heart is similar to that seen in cases of Friedreich's ataxia with cardiac involvement. The cases described in this report resemble clinically the cardiac signs and symptoms described by Evans as familial cardiomegaly. In Evans' cases cardiac enlargement or minor symptoms brought the patient to the clinic, at which time electrocardiographic abnormalities were

present. It is interesting to note and of possible significance, depending on follow-up studies, that in some ten cases discovered during routine electrocardiographic examination in apparently healthy, fit, R.C.A.F. aircrew, the men were found to have electrocardiograms with T-wave abnormalities. No explanation for these changes was found at the time; however, careful follow-up study is not yet available on all of these cases (Stewart and Manning[10]).

The familial nature of Friedreich's disease is well known, and it is apparent that cardiac manifestations occur in approximately one-third of the cases and bear a particular relaionship to those with a positive family history. The heredofamilial ataxias may appear in many variations in any particular family. The cardiac manifestations up to the present have been described only in cases of Friedreich's ataxia and, in addition to being minimized, have not been considered or shown to be the cause of death except in isolated cases. From this study it would appear that those patients with electrocardiographic changes are likely to have cardiac failure either in chronic congestive failure or as an acute cardiac death. The pathological cardiac findings in Friedreich's ataxia and in familial cardiomegaly are strikingly similar. The size of the heart was not as great in the former, but in familial cardiomegaly the cases may have come to examination late in their course. Furthermore, in Evans' and Wright's[2] Friedreich's ataxia series the clinical findings differ from the familial cardiomegaly group in that rapid ectopic rhythms did not occur. However, in our cases of Friedreich's ataxia, irregularities of rhythm occurred in three of four patients, and led to distressing cardiac signs and symptoms in two. If we accept the familial nature in both, then there is a close similarity both clinically and pathologically between Friedreich's ataxia and familial cardiomegaly. It may well be that in Friedreich's ataxia the early electrocardiographic changes merely herald the onset of eventual cardiac disorder leading to distressing ectopic rhythms, left ventricular enlargement, and eventual heart failure. It would seem reasonable to deduct that the factors responsible for Friedreich's ataxia may lead to heart disease also in one-third of the cases; in others heart disease only may result (the familial cardiac group). It may therefore be expected that the neurological manifestations might appear in some and the cardiac disorder in others.

In Friedreich's ataxia the electrocardiographic changes were discovered fortuitously after this diagnosis was well established. In the familial cardiac group (in the absence of neurological symptoms) the electrocardiographic changes may have been present for some time prior to the appearance of definite symptoms. Such reasoning may attach some significance to the finding of T-wave changes seen from time to time in apparently fit individuals on routine electrocardiographic examination. These cases may represent early examples of familial cardiomegaly. On looking back, it becomes apparent that one should reinvestigate patients in this group with particular reference being made to the family history. This of course, is at present merely a theory which, however, merits further investigation in this group.

Although the etiology remains obscure, it would appear that the lethal gene may result in true Friedreich's ataxia, Friedreich's ataxia associated with the cardiac disorders, variants of Friedreich's, and intermediate forms of the degenera-

tive processes within the central nervous system. We now have some evidence that the heart alone may be affected. The literature contains many reports of families in which various members may be affected with one or more of these variants, for example; Friedreich's ataxia and Marie syndromes and other intermediate forms can occur all within the same family. Links between hereditary ataxia and familial spastic paraplegia have also been suggested. Roth[7] and Spillane[9] showed that peroneal muscular atrophy, Friedreich's disease, and an abortive amyotrophic disorder could all result from the expression of the same gene.

Roth[7] has reviewed at some length many of the variants and intermediate forms of hereditary ataxia and has remarked on the occurrence of a wide variety of defects reported in the published cases of Friedreich's disease (mental defect, diabetes, epilepsy, deafness, congenital heart disease, etc.). Roth reports a family of special interest in that Friedreich's disease occurred in a mother and daughter and heart disease in five other members of the same family over three generations. The mother with Friedreich's ataxia had six siblings, four of whom had heart disease. Her father had died suddenly of "heart disease" at the age of 62 years and one brother of heart disease at the age of 34 years. Although the details of the cardiac disorder in these cases are not known, the close relationship between Friedreich's ataxia and heart disease in the family supports the concept that the lethal gene responsible for Friedreich's disease, its variants, and heart disease might well be responsible also for a familial cardiac disorder, thus adding additional support to the syndrome of familial cardiomegaly.

The pathological similarity previously reported between Friedreich's ataxia and familial cardiac disorders, together with the similar clinical manifestations illustrated by the cases presented in this report, the familial nature of both, the finding of such a close relationship between Friedreich's ataxia and heart disease in a single family (such as reported by Roth) give some support, it is felt, to the concept that the lethal gene may result in familial heart disease occurring alone within the heredofamilial group of disorders.

SUMMARY

Six cases of Friedreich's ataxia have been described, four of which showed classical pictures and two of which were considered to be variants of the disease. Cardiac manifestations were observed in four of these cases; in the remaining two no cardiac changes were noted; these cases, however, showed increased deep reflexes and might be considered as variants of the classical picture. Two patients were admitted to the hospital for treatment of the cardiac disorder and two cases were discovered while the patients were in the hospital during investigations of the neurological disorder.

On examination, in addition to the neurological features, a rapid, irregular heart action was noted in three patients, two of whom required treatment for Stokes-Adams-like attacks and acute heart failure. In the third case the rapid, irregular rhythm had resulted in "palpitation" and dyspnea which, however, had not become a major complaint to the patient.

In the remaining three patients there were no cardiac symptoms or signs; one of these showed the classical Friedreich's syndrome and electrocardiographic abnormalities.

The electrocardiogram revealed multiple auricular and ventricular extrasystoles in three patients, with paroxysms of tachycardia in two of these. One other patient showed only T-wave abnormalities. The remaining two were considered normal, although one showed a marked sinus arrhythmia and minor degree of right axis deviation. Four cases showed significant T-wave abnormalities resembling cardiac infarction, and these occurred in the four patients with absent deep reflexes.

A notable feature of these cases was the irregular heart action leading to cardiac insufficiency requiring treatment. This has not been a finding associated with the Friedreich's ataxia but has been reported as the principle clinical feature in familial cardiomegaly. The pathological similarity between Friedreich's disease and familial cardiomegaly is discussed, together with a review of the literature related to the heredo familial variants of Friedreich's ataxia, including a family in which both Friedreich's and heart disease has occurred.

From the cases presented in this report there is a close relationship between the cardiac manifestations of the Friedreich's Ataxia and familial cardiomegaly. The pathological similarity, the familial nature, and similar clinical features of both, together with the known variants of the Friedreich group, including families with both Friedreich's ataxia and heart disease (in different members), support the concept that the lethal gene (or faulty germinal mutation) may result in familial heart disease occurring alone within the heredofamilial group of disorders.

ADDENDUM

Since the presentation of this report, Hejtmancik, Bradfield, and Miller have described two cases of "myocarditis" in Friedreich's ataxia. In both cases a rapid, irregular sinus rhythm due to frequent ectopic beats was observed, similar to the findings noted in this communication. The electrocardiographic findings otherwise were similar to those already described. (AM. HEART J. **38**:757, 1949.)

I wish to thank Dr. William Evans, London Hospital, Whitechapel, for permission to publish the findings in Case 3.

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II. THE FORM OF THE QRS COMPLEX IN BUNDLE BRANCH BLOCK AND IN ANTEROLATERAL INFARCTION

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THE difficult task of elucidating fundamental concepts as to the form and interrelations of the component phases of the QRS complexes in the six Wilson precordial leads has been facilitated by use of a series of diagrams reconstructing the portion of the QRS complex registered in each lead during fixed intervals after the onset of the initial deflection. The use of this diagrammatic method of analysis of the precordial electrocardiogram in the normal, as well as in left and right ventricular hypertrophy, has been reported.[1] The purpose of this communication is to illustrate its employment to bring out the characteristic features of the QRS complex in bundle branch block and in anterolateral myocardial infarction.

Left Bundle Branch Block.—In Fig. 1, the electrocardiogram of a patient with advanced hypertensive heart disease is reproduced and analyzed by means of a set of four diagrams, which reconstruct the QRS complex as registered during the first 0.02, 0.04, 0.08, and 0.12 second, respectively. The diagram of the ventricles differs from those of the previous article[1] in that a coronal rather than a transverse section is employed in order to depict the bundle of His and its right and left branches. The transitional zone is situated between the V_4 and V_5 positions, so that the first four precordial leads reflect principally the potential variations of the epicardial surface of the right ventricle; the last two leads, those of the left ventricle.

A hasty comparison of Leads V_1, V_2, V_5, and V_6 with the corresponding leads of a patient with electrocardiographic findings typical of left ventricular hypertrophy (Fig. 2 of the previous article[1]) reveals a superficial resemblance in respect to the relative amplitudes of the R and S waves, the displacement of the RS-T junctions and the direction of the T waves. The most significant differences between the two tracings will be found in the duration of the QRS complex, and in the contour of this complex in Leads V_5 and V_6. These features require detailed consideration.

The QRS interval of 0.13 second in association with a sinus rhythm and P-R interval exceeding 0.12 second establishes the presence of an intraventricular conduction defect. A comparison of the time interval preceding the onset of the intrinsicoid deflection in leads over the right with that in leads over the left ventricle reveals the ventricle through which conduction is delayed. The fact that a mere 0.02 second is required for the attainment of the peak of the R wave

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in the first four precordial leads and for the inscription of the intrinsicoid deflection in Lead V_1 signifies early onset and completion of right ventricular activation. Hence, the lesion responsible for the prolongation of the QRS interval is not located in the right ventricle. On the other hand, the precipitous downstroke representative of the intrinsicoid deflection in Leads V_5 and V_6 does not begin until 0.08 second after the onset of the QRS complex, indicating an abnormal delay in arrival of the impulse at the epicardial surface of the anterolateral wall of the left ventricle. Therefore, the prolongation of the QRS interval is caused by a conduction defect in the left ventricle.

The decision as to whether the conduction defect is in the septum or free wall of the left ventricle is made from the direction of the initial phase of the QRS complex, together with the contour of the rest of the tracing preceding the delayed intrinsicoid deflection. If the prolongation of the QRS interval in this tracing were the result of a conduction defect limited to the outer wall of the left ventricle, Leads V_5 and V_6 should have displayed a Q wave, representing negative cavity potentials derived from impulses passing from left to right through the septum[1] and transmitted to the left axilla up until the beginning of activation of the anterolateral wall. Furthermore, if the conduction delay were referable to a lesion in the subendocardial layer of the anterolateral wall, an abnormally deep and prolonged Q wave should have been present, as a reflection of the longer interval between the spread of the impulse through the septum and its arrival in responsive muscle in the free wall. This situation will be exemplified in Fig. 3. If the lesion of the outer wall spared the subendocardial layer, but involved the midzone, a normal Q wave, followed by a notched or slurred upstroke, would have been expected. A Q wave, preceding a notched or slurred R wave in leads facing the epicardial surface of the left ventricle, would be interpreted as evidence (1) that the septum was activated in the normal fashion, (2) that the conduction defect responsible for the distortion of the R wave was located in the outer wall.

The foregoing patterns must be distinguished from the double upstroke with intervening notching or slurring recorded in V_5 and V_6 of Fig. 1. The registration of an initial R rather than a Q wave in all precordial and unipolar limb leads with a late intrinsicoid deflection indicates early positivity of the left ventricular cavity, due to septal activation by impulses passing from right to left, as shown by the arrow in Fig. 1, *a*. The secondary upstroke, beginning at the nadir of the notch 0.04 second after the onset of the QRS complex, marks the arrival of the impulse in the outer wall of the left ventricle. Septal activation from right to left, together with abnormal delay in arrival of the impulse in the outer wall of the left ventricle, establishes the presence of left bundle branch block.[2,3,4]

The time elapsing between the onset and peak of the secondary upstroke in V_5 and V_6 constitutes a rough index of the time consumed in passage of the impulse from the endocardial to the epicardial surface of the anterolateral wall of the left ventricle. The 0.04 second interval in this case is borderline and not diagnostic of the left ventricular hypertrophy evident on physical examination. The registration of distinct S waves following the intrinsicoid deflections in Leads V_5 and V_6 constitutes evidence of continuing activation of more lateral or pos-

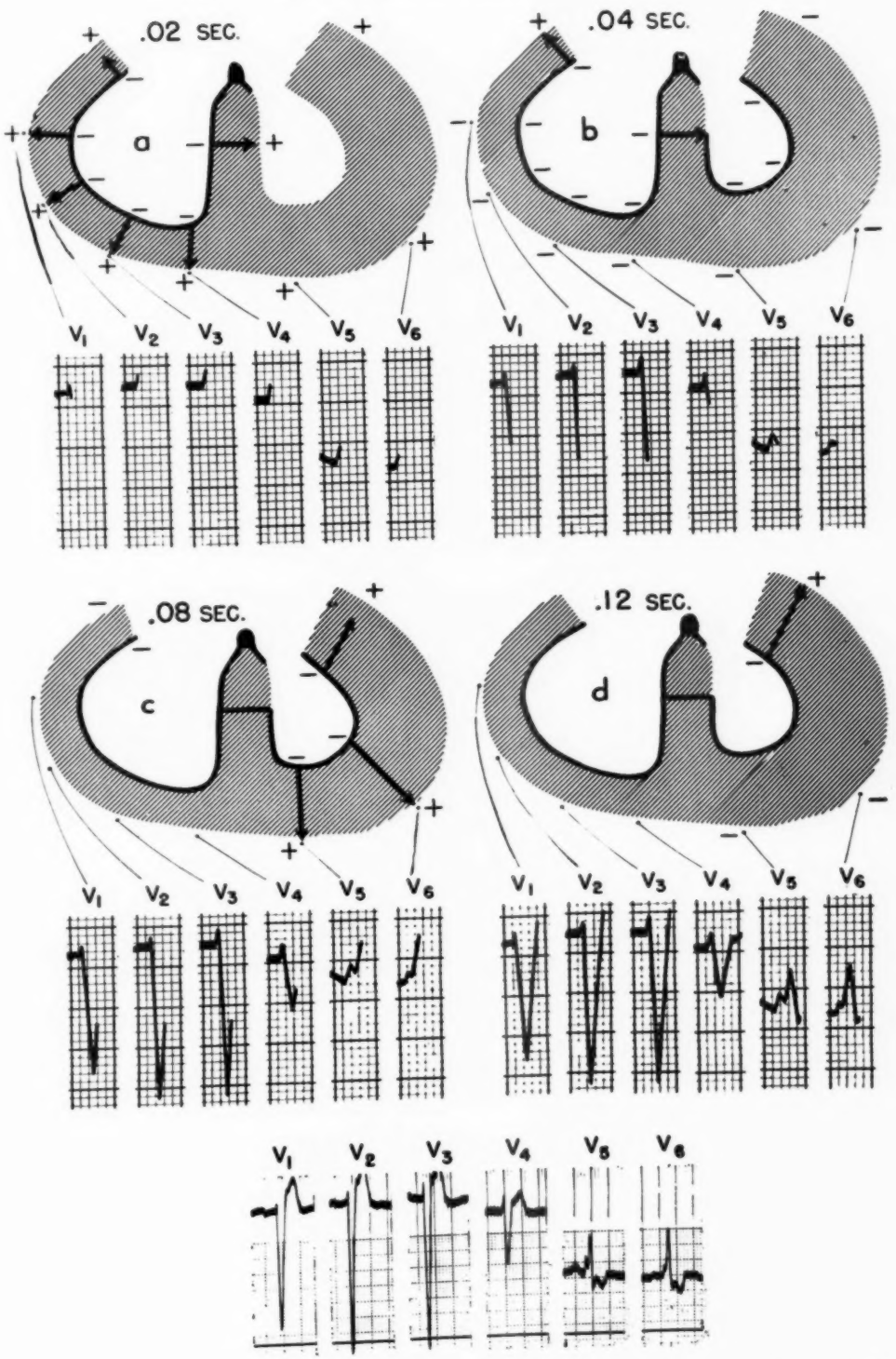

Fig. 1.—Precordial electrocardiogram in left bundle branch block. Diagrammatic reconstruction of the portion of the QRS complex registered in each lead and the probable status of ventricular activation at intervals of 0.02, 0.04, 0.08, and 0.12 second after the onset of the initial deflection.

terior portions of the left ventricle after completion of depolarization of the anterolateral wall, as depicted in Fig. 1, *d*. It is, therefore, probable that leads from the esophagus or back would have shown an abnormally prolonged secondary upstroke, representative of hypertrophy and/or delayed conduction in the posterior or lateral wall. Activation of the free wall of the left ventricle not only produces the secondary upstroke in Leads V_5 and V_6, but also contributes to the deep, broad S waves simultaneously registered in right ventricular leads (Fig. 1, *c*).

Thus, a diagnosis of left bundle branch block is reached in Fig. 1, through the demonstration of: (1) a normal P wave and P-R interval of 0.12 second or more, signifying that the impulse which has caused the QRS complex was of auricular origin and reached the ventricles through the auriculoventricular node; (2) a QRS interval of 0.12 second or more, which denotes a conduction defect somewhere in the ventricles; (3) an early attainment of the peak of the R wave in right ventricular leads and an abnormally late attainment in left ventricular leads, indicating that the spread of the impulse was normal through the right ventricle and delayed through the left ventricle; and (4) an initial upright deflection in left ventricular leads, signifying that the conduction defect was in the left bundle branch, rather than in the outer wall of the left ventricle. The depression of the RS-T junctions and inversion of the T waves in left ventricular leads and the elevated RS-T junctions and upright T waves in right ventricular leads constitute the usual findings in left bundle branch block. The RS-T displacement in this case was exaggerated as a result of digitalis action.

Right Bundle Branch Block.—The precordial electrocardiogram of a patient with long-standing femoral arteriovenous aneurysm is reproduced in Fig. 2. An attempted closure nine years previously was unsuccessful and further surgery was refused. Serial limb leads over this period showed a first degree auriculoventricular block and no significant changes in the QRS-T pattern. At autopsy, marked right ventricular hypertrophy and moderate left ventricular hypertrophy were demonstrated.

The tracing is analyzed in a series of four diagrams, which reconstruct the QRS complex as it was registered in each lead during the first 0.02 second, 0.04 second, 0.08 second, and 0.12 second, respectively. In these diagrams, as in Fig. 1, a coronal section of the ventricles is employed, in order to depict the bundle of His and its right and left branches.

A sinus rhythm and a constant P-R interval of 0.28 second without dropped beats are present. The QRS interval of 0.16 second is the most striking feature of the tracing and, in view of the rhythm, establishes the presence of an intraventricular conduction defect.

A study of the R/S relationships in the six precordial leads reveals that the broad, double peaked R and narrow S waves recorded in V_1 and V_2 contrast sharply with the narrow R and wide, slurred S waves in V_3, V_4, V_5, and V_6. Thus, the transitional zone is situated between the V_2 and V_3 positions, the first two leads reflecting principally the potential variations of the epicardial surface of the right ventricle, the last four leads depicting chiefly the potential variations of the epicardial surface of the left ventricle.

The initial upstroke in Leads V_3, V_4, V_5, and V_6 (Fig. 2, *a*), together with the attainment of the peak of the R wave in these leads within 0.04 second (Fig. 2, *b*), denotes early onset and relatively early completion of activation of the anterolateral wall of the left ventricle and shows that the conduction

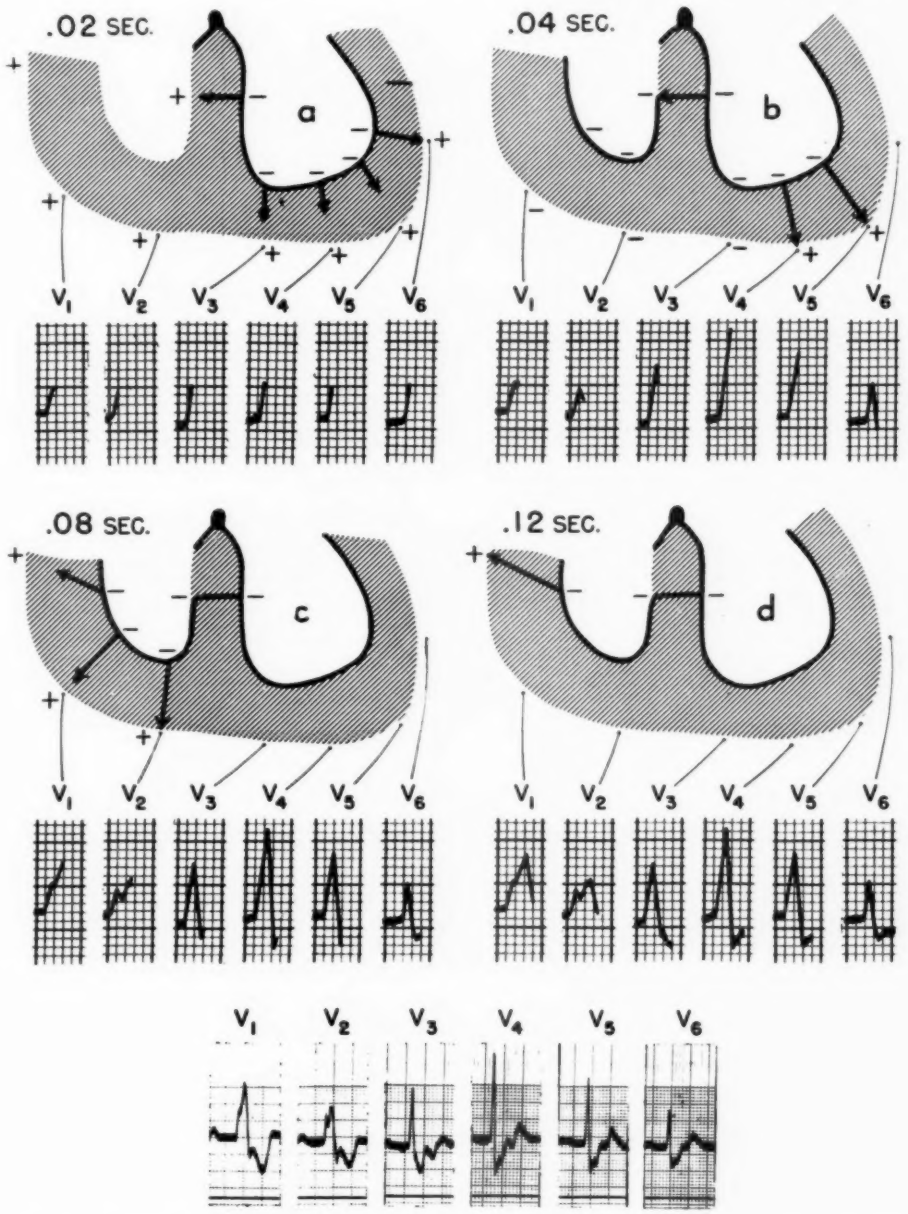

Fig. 2.—Precordial electrocardiogram in right bundle branch block. Diagrammatic reconstruction of the portion of the QRS complex registered in each lead and the probable status of ventricular activation at intervals of 0.02, 0.04, 0.08, and 0.12 second after the onset of the initial deflection.

defect responsible for the QRS prolongation is located elsewhere. The fact that the intrinsicoid downstroke in Leads V_1 and V_2 begins 0.08 second or more after the onset of the QRS complex places the conduction defect in the right ventricle.[3,5,6]

The nature of the defect is revealed through a study of the portion of the tracing preceding the late intrinsicoid deflection in Leads V_1 and V_2. The registration of an initial R wave in these leads indicates septal activation by impulses spreading from left to right, as depicted by the arrow in Fig. 2, *a*; the secondary upstroke, following a notch or coarse slurring, is referable to passage of the impulse through the free wall of the right ventricle, as shown by the arrow in Fig. 2, *c*. The interval of 0.04 second between the onset of activation of the septum (or beginning of the initial R wave) and the onset of activation of the free wall of the right ventricle (beginning of the second R wave) is abnormally long and establishes the presence of right bundle branch block. Since an interval of 0.04 second or more is required for passage of the impulse from the endocardial to epicardial surface of the right ventricle (Fig. 2, *c*), it is evident that conduction through the outer wall of the right ventricle is likewise impaired in this patient, presumably due, at least in part, to the right ventricular hypertrophy which was demonstrated at autopsy. An even longer time was apparently consumed in the activation of more lateral or posterior portions of the right ventricle, as may be inferred from the presence of S waves in Leads V_1 and V_2.

During the period between 0.04 and 0.08 second, when the R wave is being registered in V_1 and V_2, the intrinsicoid deflection is completed in Leads V_3, V_4, V_5, and V_6 and is followed by a broad, slurred S wave, due to transmission of negative right ventricular cavity potentials through the completely activated septum to the left precordium and axilla. The opposing potentials from the hypertrophied right ventricle may have accounted for the fact that the R wave in left ventricular leads was not as great in amplitude or duration as might have been expected from the degree of left ventricular hypertrophy found at autopsy.

The depressed RS-T junctions and inverted T waves in right ventricular Leads V_1 and V_2 and the upright T waves in left ventricular Leads V_5 and V_6 constitute the usual findings in right bundle branch block. The diphasic T waves in the intervening leads are transitional in type.

Anterolateral Myocardial Infarction.—Fig. 3 presents an analysis of the precordial electrocardiogram obtained on a 35-year-old woman approximately two years after an acute myocardial infarction and about six months prior to death. Autopsy revealed a completely healed anterolateral infarct, occupying the area left unshaded in the diagram. The electrocardiogram is analyzed through a series of four drawings, which reconstruct the portion of the QRS complex registered in each lead during the first 0.02, 0.04, 0.06, and 0.08 second, respectively.

Leads at either end of the precordium show contrasting patterns, the rS deflection in Lead V_1 representing chiefly the potential variations of the epicardial surface of the right ventricle, the qR complex in V_6 reflecting the potential variations of the lateral wall of the left ventricle. The sharp intrinsicoid downstroke in the upright P wave recorded in Lead V_1 suggests that the electrode was in the

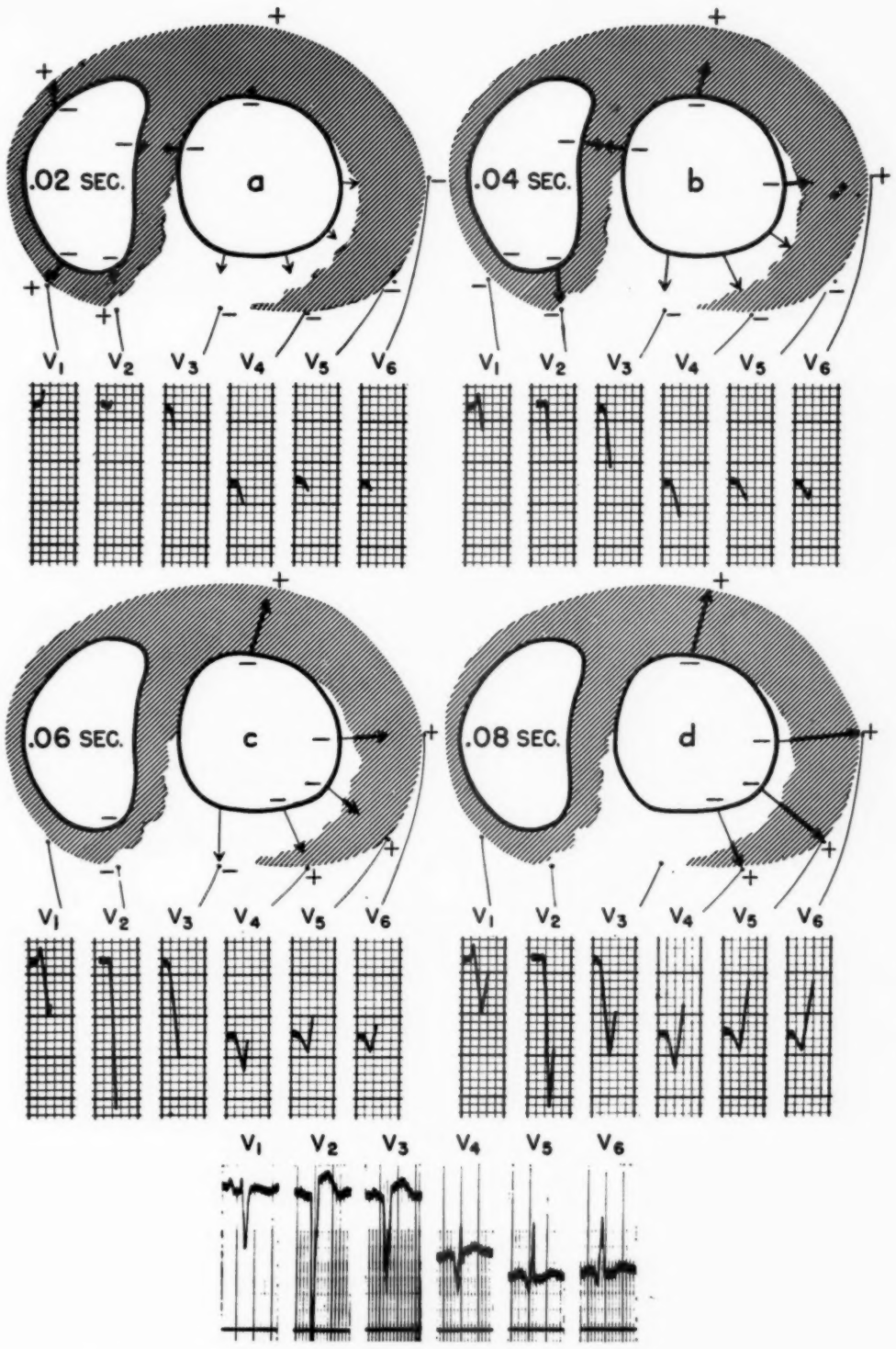

Fig. 3.—Precordial electrocardiogram in anterolateral infarction. Diagrammatic reconstruction of the portion of the QRS complex registered in each lead and the probable status of ventricular activation at intervals of 0.02, 0.04, 0.06, and 0.08 second after the onset of the initial deflection. The portion of the wall left unshaded marks the position of the healed infarct found at autopsy. The activation of intact muscle is represented by the use of a heavy shafted arrow for the activating impulse, and by the registration of positive potential at the epicardial surface, as contrasted with negative potential in the cavity; the failure of activation of infarcted muscle is indicated by the use of a light shafted arrow and by the registration of negative potential at the epicardial surface, comparable to that in the cavity.

vicinity of the tricuspid ring. The minute initial R wave preceding the deep, broad S wave in Lead V_2 indicates that the electrode was still on the right ventricular side of the septum. The QS deflection in Lead V_3 was transitional between the rS patterns in V_1 and V_2 and the qR patterns in V_4, V_5, and V_6, suggesting that the electrode was near the septum, but probably on the left ventricular side. Although Leads V_4, V_5, and V_6 differ in respect to QR ratio, they show a synchronous late intrinsicoid deflection of left ventricular origin. Leads V_5 and V_6 of this case are comparable to the corresponding leads of Case 1, Fig. 1, in prolongation of QRS interval to 0.12 second and in the delay in onset of the intrinsicoid deflection to 0.08 second, but differ significantly in respect to the direction of the initial deflection. The significance of the latter in localizing the conduction defect will be brought out subsequently in the analysis of the tracing.

In Lead V_1, the initial deflection is upright and rises 3.5 mm. to reach its peak by the end of 0.02 second. This represents a normal finding for precordial leads overlying the right ventricle and is in keeping with the demonstration of a normal anterolateral right ventricular wall at autopsy. Attention is directed to the marked reduction of the R wave in Lead V_2 in comparison with its counterpart in V_1. As the electrode is moved from the V_1 to the V_2 position, an increase in the amplitude of the R wave is expected because of closer proximity of the electrode to the septum and left ventricle. The decrease is an abnormal finding and may occur under the following circumstances: (1) infarction of septum and/or anteroseptal wall of the left ventricle, with consequent loss of positive potentials transmitted from this portion of the heart to the neighboring V_2 position; (2) disproportion between the muscle mass at the tricuspid orifice (near position V_1) and that forming the anteroseptal wall of the right ventricle (near position V_2), due either to preponderant hypertrophy of the muscular tricuspid ring or to infarction or other destructive lesion of the anteroseptal aspect of the right ventricle. The former alternative is responsible for the reduction in the initial R wave in Lead V_2 of this case, as is shown by the abnormal Q patterns in precordial leads over the left ventricle and subsequently confirmed at autopsy.

A Q wave is recorded in left ventricular Leads V_3, V_4, V_5, and V_6 (Fig. 3, *a*), indicating initial negativity of the left ventricular cavity, due to early activation of the left side of the septum by impulses distributed through the left Purkinje plexus. This finding excludes uncomplicated left bundle branch block as a cause of the delayed intrinsicoid deflection in the last three precordial leads and the prolongation in the QRS interval. Although Q waves may be recorded in left ventricular leads when left bundle branch block is complicated by almost complete infarction of the septum,[3] this possibility is excluded in the present case by the fact that (1) the QRS interval is only 0.12 second; (2) the Q wave is longer in duration in left ventricular Leads V_3, and V_4, which are relatively near the right ventricle, than in V_6, which is far removed.

A study of Fig. 3,*b* shows that the initial downstroke continues beyond the normal limit of 0.02 second in each of the last four precordial leads. In Lead V_3, the tracing describes a smooth downward course for at least 0.06 second, then returns to the isoelectric line, thereby completing an unnotched QS deflection

(Fig. 3,*c* and *d*). The lack of an initial or final R wave, together with the absence of a notch on either limb of this QS deflection, would suggest that the anteroseptal wall of the left ventricle, subtended by the electrode at V_3, is unresponsive to the activating impulse. In view of the normal R wave in Lead V_1 and the abnormal QR deflection in Leads V_4, V_5, and V_6, the QS deflection at V_3 may be interpreted as evidence of a central zone of transmural infarction,[7,8,9,10,11] a conclusion subsequently confirmed at post-mortem examination. Under such circumstances, the ventricular wall merely serves as a window for the transmission of negative cavity potentials to the surface. The downstroke of the QS is initiated by negative potentials transmitted to the cavity during activation of intact portions of the septum and is continued by negative potentials derived from the posterior and intact portions of the lateral wall of the left ventricle. The ascending limb of the QS deflection begins when activation of the outer wall of the left ventricle ceases or when the forces developed by activation of remaining muscle are too small to make the cavity more negative. The synchrony of the lower portion of the downstroke, apex, and upstroke of the QS deflection in Lead V_3 with the S wave in Leads V_1 and V_2 suggests a common origin. The continuation of the ascending limb above the isoelectric line to an elevated RS-T junction may reflect beginning repolarization of the intact portions of the septum or right ventricle.

The downstroke of the Q wave continues for an interval of 0.03 second in Lead V_6 and for 0.04 second in V_4 and V_5, when it is replaced by an upstroke (Fig. 3,*c*). The transmission of cavity potentials through the anterolateral wall of the left ventricle for 0.03 second or longer is abnormal and occurs when the subendocardial layer fails to respond to the activating impulse. The usual cause is subendocardial infarction. Since the cavity is showing increasing negativity during the first 0.06 second (as evidenced by the continuing downstroke in V_1, V_2, and V_3), the earlier reversal in the direction of the string in V_4, V_5, and V_6 marks the arrival of the impulse in responsive muscle in more superficial portions of the anterolateral wall. The activation of subepicardial muscle is confirmed by the fact that the upstroke crosses the isoelectric line to form a distinct late R wave (Fig. 3, *d*). The time interval of 0.04 second to 0.05 second elapsing between the onset and peak of the late R wave is abnormally long for activation of the remaining myocardium and may be due to hypertrophy and/or patchy extension of the infarct into the subepicardial layer. Thus, the lateness of the intrinsicoid deflection and prolongation of the QRS interval are attributable to a lesion of the anterolateral wall and are in part due to a temporary arrest of the impulse in an infarcted supendocardial layer, in part to a longer time required for activation of the more superficial layers because of hypertrophy or patchy infarction.

The Q waves in Leads V_4 and V_5 are abnormal, not only in duration, but also in amplitude relative to that of the succeeding R waves. This is revealed by increased QR ratios of 100 per cent and 33 per cent, respectively, in Leads V_4 and V_5. Although the time interval from onset to nadir of the Q wave in V_6 is sufficiently long to suggest subendocardial infarction, the QR ratio has only a

borderline value of 25 per cent, probably due to increase of the R wave as a result of hypertrophy of the more superficial layers.

QR patterns in left precordial leads characterized by a downstroke 0.03 second or longer in duration and more than 25 per cent of the amplitude of the succeeding R wave are characteristic of subendocardial infarction and are recorded at the margins of a transmural infarct, due to the tendency for such lesions to extend much farther on their endocardial than on their epicardial surface.[7,8,10,11] A rough estimate of the relative thickness of the infarcted subendocardial and living subepicardial layer may be made from (1) the time from onset to nadir of the Q, as compared with the time from onset to peak of R, and (2) the relative amplitudes of the Q and R waves. The equality of the Q and R deflections in Lead V_4, both as to duration and amplitude, suggests that the infarct involved approximately the subendocard al half of the subjacent anterolateral wall. The progressive decrease in duration and amplitude of the Q in reference to the R wave, as the electrode was moved to the V_5 and V_6 positions, suggests a progressive thinning of the subendocardial infarct as it extended from the anterior into the lateral wall. These deductions are in keeping with the anatomic distribution of the infarct found at autopsy and illustrated in the diagram.

The T wave pattern proved fixed in serial tracings. The elevated RS-T junctions and upright T waves, recorded in Leads V_3 and V_4, are not uncommon fixed residues in leads over extensive healed infarcts.

SUMMARY

The form and interrelations of the component phases of the QRS complexes in the six Wilson precordial leads are demonstrated through a diagrammatic reconstruction of the portion of the QRS complex registered in each lead at fixed intervals after the onset of the initial deflection. This method of analysis is offered as a teaching aid and is employed to bring out the characteristic features of the QRS complex in left bundle branch block, right bundle branch block, and anterolateral myocardial infarction.

The illustrations were made by Miss Evelyn Erickson, assisted by Miss Geraldine Chesney.

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INVISIBLE CONDUCTION LEADING TO ERRORS IN ELECTROCARDIOGRAPHIC INTERPRETATION

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IN THEIR extensive studies on concealed A-V nodal conduction, Langendorf and Mehlman[1,2] reported many new instances demonstrating the effect of blocked A-V nodal impulses on subsequent impulse conduction. On one occasion an unusual phenomenon was seen, namely, a sudden prolongation of the P-R interval for just one beat. This was explained on the assumption of an interpolated and blocked (nonconducted) A-V nodal premature systole, which had the same effect on a subsequent beat as a conducted interpolated beat, thus "imitating" first-degree block.[1]

The present paper is presented for two reasons: first, to demonstrate a case which showed this phenomenon repeatedly; and second, to report a few instances in which invisible A-V nodal and retrograde auricular conduction, limited to Lead I, could be demonstrated. Failure to recognize this invisible conduction in Lead I may result in wrong interpretation of cardiac irregularities caused by blocked auricular and A-V nodal premature beats.

The electrocardiograms shown in Figs. 1, 2, and 3, were taken of a patient 55 years of age who was known to have cardiac irregularities for 15 years. There was no history of rheumatic fever but, when he was 30 years of age, he had had typhoid fever. Although he often felt some unusual sensation in his chest, such as jumping, "flutter," and occasionally palpitation with choking, he was not bothered by these sensations and was in no way incapacitated as a truck-driver. Physical examination revealed cardiac irregularity but no other evidence of heart disease.

Fig. 1 shows a regular sinus rhythm. The P-P interval measures 64/100 second. In the upper tracing (Lead II), the first sinus beat is followed by an inverted P wave without a ventricular response. The retrograde contour of the P wave, together with the compensatory pause, points to a blocked premature A-V nodal beat. In the lower strip (aV_L) a conducted premature A-V nodal beat without visible inverted P wave follows the first sinus beat at a distance which is identical to the coupling-time of the blocked P wave in the upper strip. Following the long pause, a group of seven beats are seen in the upper strip. The last beat of this group again is followed by a blocked premature A-V nodal beat, after which the same group repeats in a rhythmic fashion. The same phenomenon is seen in the lower strip except that the last beat in the series is a conducted premature beat with aberration.

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In spite of the very regular P-P intervals, the distances between the R-R complexes are not so regular. Within one group containing six sinus beats, the R-R intervals measure 0.64, 0.69, 0.58, 0.70, 0.64 second. The interval R_4-R_6 contains an interpolated A-V nodal premature beat which explains the slight prolongation of this ventricular interval. The P wave of the sixth beat is superimposed on the T wave of the interpolated beat. The following P-R interval, although it cannot be accurately measured, is definitely longer than the normal P-R interval of 0.16 sec.; it is approximately 0.24 second.

The prolongation of a ventricular interval which contains an interpolated premature beat is well known and is explained by the fact that the sinus beat which follows the interpolated extra beat, finds the junctional tissue still affected by the preceding impulse. The result is a prolongation of the following P-R interval and consequently also a late appearance of the R wave.

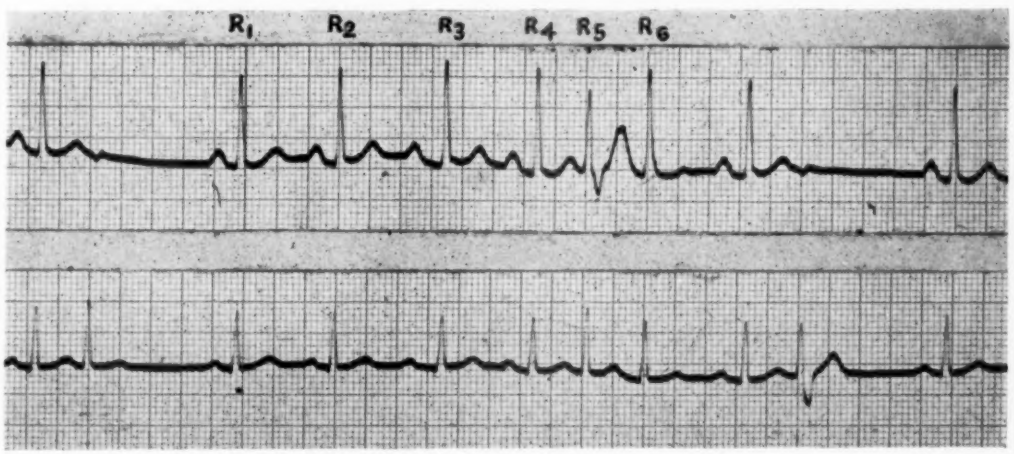

Fig. 1.—Case 1, showing different types of block in A-V nodal conduction. Within the R_2-R_3 interval there is a prolonged P-R interval. This is the result of an invisible, blocked, and interpolated premature A-V nodal beat. (Discussed in text.)

Exactly the same time relations as those during the R-R interval, which contains the interpolated beat, are seen within the R_2-R_3 interval, although an interpolated beat is not visible. The R_2-R_3 distance is 0.69 sec., the P-R distance within the R_2-R_3 interval measures 0.24 second. This fact points to the existence of a similar mechanism within both these R-R intervals (R_2-R_3; R_4-R_6) and is strong evidence of the presence of an interpolated and blocked premature A-V nodal systole within the R_2-R_3 interval which is blocked in both directions, retrograde and antegrade. The invisible interpolated and blocked premature A-V nodal beat exerts the same effect on a subsequent beat as a conducted interpolated beat. The prolonged P-R interval following the blocked beat simulates first degree A-V block.

In Langendorf and Mehlman's case, which showed this prolonged P-R interval on only one occasion, the diagnosis was based on the occurrence in the same record of typical A-V nodal premature systoles and of blocked P waves

of retrograde contour. The present case, which displays the same time relations during R-R intervals containing a conducted interpolated beat and the R-R intervals without an interpolated beat, together with the presence of blocked A-V nodal premature beats with retrograde P waves in the same record, presents definite proof of the correctness of Langendorf and Mehlman's assumption.

In Fig. 1 three different types of block of A-V nodal conduction are present. The first premature beat with the retrograde P wave is blocked in ventricular direction; the conducted interpolated beat (R_5) is blocked in auricular direction, and the concealed and interpolated A-V nodal premature beat (within the R_2-R_3 interval) is blocked in both directions, antegrade and retrograde. It is of some interest that the premature beats, regardless of the direction in which they are blocked, always appear in the form of trigemini. The trigeminal rhythm, however, is disguised because of the blocked invisible A-V nodal beats.

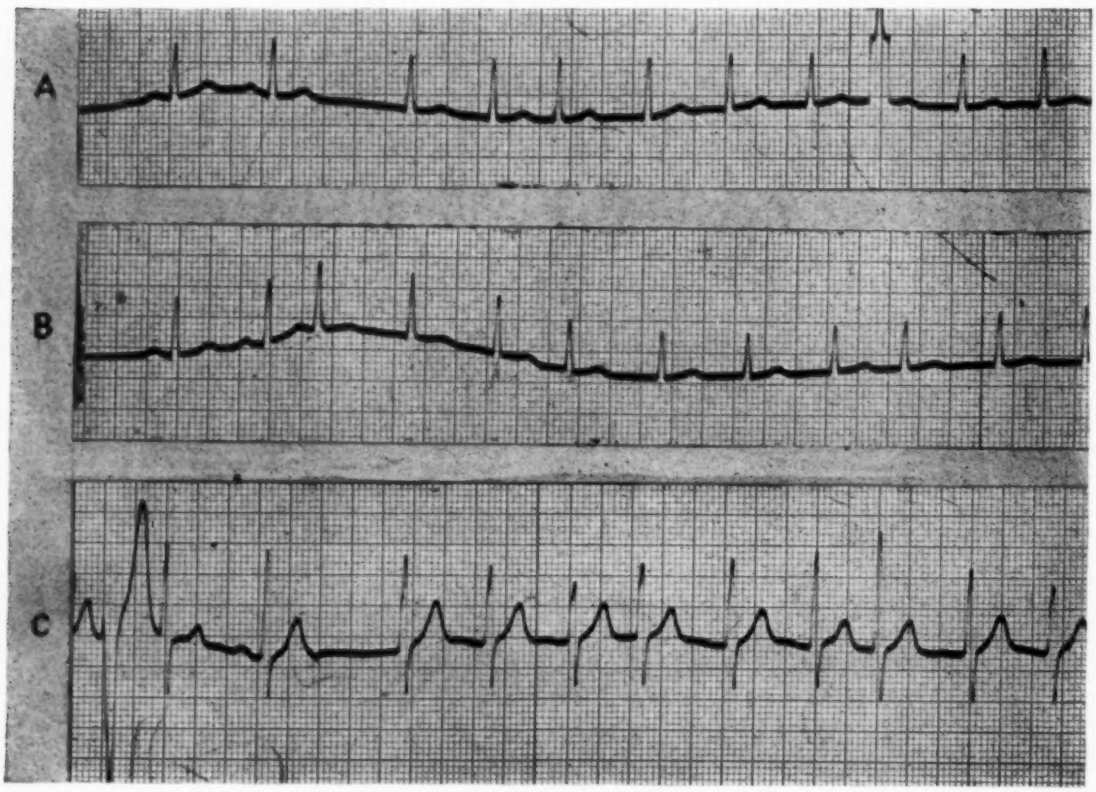

Fig. 2.—Case 1. *A* **represents Lead I;** *B*, **Lead aV_L; and** *C*, **Lead V_4. Following the first two sinus beats in** *A* **there is an invisible blocked A-V nodal premature beat. (Discussed in text.)**

Another interesting feature which is seen repeatedly in Case 1 is the start of the paroxysmal A-V nodal tachycardia. This is illustrated in Fig. 2,*A*, in which there are two sinus beats and then, following a longer pause, a slightly irregular A-V nodal tachycardia is initiated. After every third or fourth beat,

a premature nodal beat appears which imitates a trigeminal or quadrigeminal rhythm within the tachycardia.

The long pause after the two sinus beats suggests that there is some type of sinus depression present which allows a pacemaker from a lower center to come into play. Under such circumstances it is usual to find a passive ectopic rhythm with a rate slower than the sinus rhythm. The frequency of the A-V nodal rhythm is faster, however, than the sinus rhythm. This points to an active ectopic rhythm. It is noteworthy that an active ectopic rhythm does not require a preceding sinus depression since the active rhythm can appear at any time following the refractory period of the preceding sinus beat.

The clue for the explanation of this apparent discrepancy is obtained by the comparison of strip *A* with the other strips in Fig. 2. The beginning of the paroxysm started in the same manner on many occasions but in *B* (Lead aV_L), the paroxysmal attack starts with the first premature A-V nodal beat. Here the distance between the sinus beat and the nodal beat which follows the premature A-V nodal beat is identical in length to the distance between the last sinus beat and the first A-V nodal beat which initiates the tachycardia in A. This is strong evidence that the real paroxysm in A does not start with the first visible A-V nodal beat but with an apparently blocked A-V nodal beat. This blocked A-V nodal beat, although not visible, can be timed in relation to the visible premature beat which initiates the A-V nodal rhythm in *B*. Strip *A* was taken in Lead I. It is a familiar fact that the pattern of retrograde conduction is not well-demonstrated in Lead I. The retrograde P wave is usually indiscernible; that is, it is practically isoelectric or slightly upright or diphasic. Consequently, the A-V nodal beat, which is blocked in antegrade direction and which initiates the paroxysm (*A*), does not give any electrocardiographic evidence in Lead I. Thus at first glance this record suggests a sinus depression and also that the attack starts with the first visible conducted beat instead of with the invisible blocked A-V nodal premature beat (*A*). Strip *C* proves the correctness of this assumption. In this strip, an inverted P wave without ventricular response follows the sinus beat at a distance of 0.35 second. This blocked premature A-V nodal beat represents the beginning of the paroxysm. This case shows that Lead I is not a suitable lead for the analysis of the phenomenon caused by blocked A-V nodal premature beats.

The tracing in Fig. 3 (Lead I) taken on the same patient illustrates again how easily an error in interpretation may occur. There is a trigeminal rhythm brought about by premature A-V nodal beats. This rhythm is once interrupted by a long sinus pause with a P-P interval measuring exactly twice the normal sinus period which is indicative of a 2:1 S-A block. The premature A-V nodal beats, one of them showing aberration, are followed by a compensatory pause. The P-P intervals which contain a premature A-V nodal beat are identical in length to the long pause which appears to be due to a 2:1 S-A block. Since the pattern of retrograde conduction does not reflect well in Lead I, it is probable that the long sinus pause represents a pseudosinus block caused by an invisible, blocked, premature A-V nodal beat with compensatory pause. The invisible retrograde A-V nodal conduction in Lead I simulates the picture of a 2:1 sino-

auricular block. Proof of this assumption is the fact that the long sinus pauses were never seen except in Lead I; whereas the pattern of retrograde conduction with block in antegrade direction was seen repeatedly in Lead II,V_4. (Figs. 1 and 2.) The trigeminal rhythm seems to be interrupted when the long sinus pause appears. Actually this rhythm is still present, but concealed because of the invisible blocked premature beat.

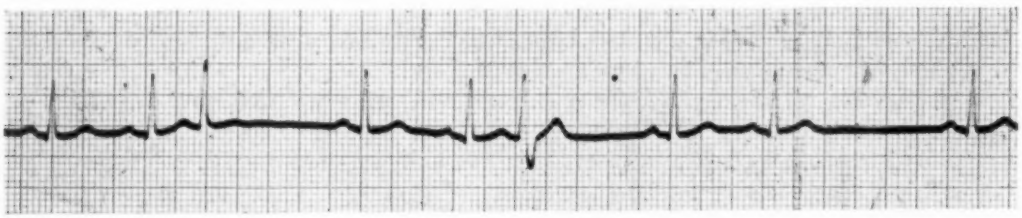

Fig. 3.—Case 1. Lead I. The trigeminal rhythm seems to be interrupted by a 2:1 S-A block. Analysis, however, proves a pseudosinus block caused by an invisible blocked A-V nodal beat.

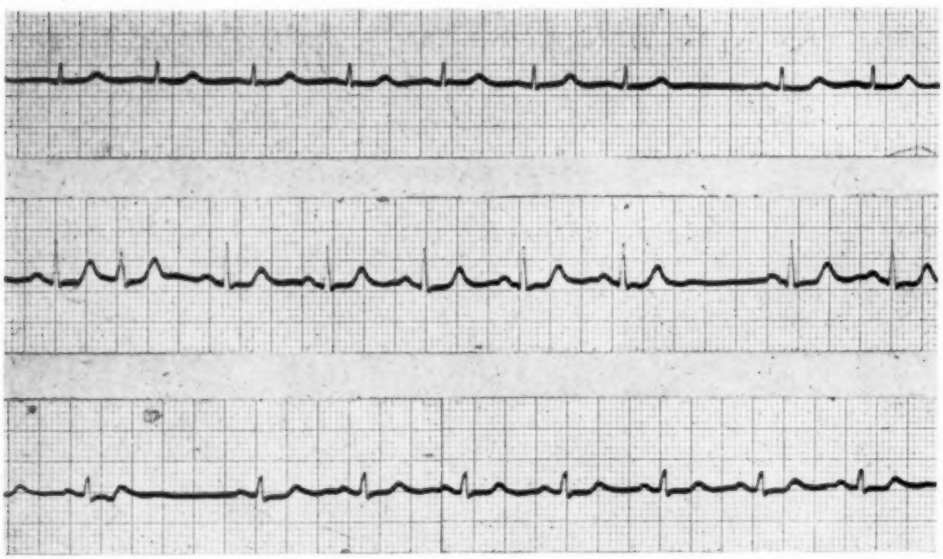

Fig. 4.—Case 2. Sinus depression in Lead I, imitated by an invisible blocked auricular premature beat. In Leads II and III, however, the inverted P wave of the blocked auricular premature beat is well seen in the ST segment of the sinus beat which precedes the long pause.

Another instance in which this type of concealed conduction is limited to Lead I, is illustrated in Fig. 4. This electrocardiogram was obtained from a woman 55 years of age who complained of slight dizziness and occasional cardiac palpitation. Physical examination did not reveal any abnormality except for the cardiac irregularity. In the upper strip a normal sinus rhythm is once interrupted by a long sinus pause which measures 100/100 second. A pause of

almost the same length is also seen in Leads II and III but in Lead II, within this pause, there is a suggestion of an inverted P wave and, in Lead III a definite inverted P wave is visible in the ST segment of the sinus beat. The R-P distance measures 0.16 second. The retrograde P waves present blocked auricular premature beats. On other occasions (Lead II), these retrograde P waves were followed by ventricular responses with delayed antegrade conduction and aberration. The retrograde conducted P waves, which are seen in Leads II and III, are not visible in Lead I. This invisible pattern of blocked premature auricular beats with preserved retrograde conduction in Lead I simulates a sinus depression.

SUMMARY AND CONCLUSIONS

Tracings of two cases are reported which show unusual types of concealed conduction. In Case 1 premature A-V nodal beats were present, some of which showed a block in an antegrade direction, some in a retrograde direction, and still others showed block in both directions. The well-known changes which were seen after an interpolated premature A-V nodal beat, namely, the prolongation of the P-R interval and a slight delay of the following R wave, were demonstrated in R-R intervals which did not contain a visible interpolated beat. This proves the presence of a blocked (invisible) interpolated premature A-V nodal beat with a block occurring in both directions. This blocked and interpolated premature beat "imitated" the pattern of first-degree A-V block.

In both Cases 1 and 2, another type of invisible conduction was observed which was strictly limited to Lead I. Blocked premature auricular or A-V nodal beats did not appear in Lead I; in the other leads, however, the blocked premature beats were easily recognized by inverted P waves without ventricular response. This was explained by the fact that frequently the pattern of retrograde conduction is not reflected in Lead I. This lack of electrocardiographic evidence in Lead I may lead to errors in interpretation of cardiac arrhythmias caused by blocked premature auricular and A-V nodal beats. In the reported cases this invisible conduction in Lead I simulated sinus depression, 2:1 S-A block, which masked the beginning of an A-V nodal tachycardia following a sinus rhythm and gave the erroneous impression of interrupting a trigeminal rhythm.

Lead I is not always suitable for the interpretation of arrhythmias caused by blocked premature auricular or A-V nodal beats. A longer sinus pause or a 2:1 S-A block, when seen only in Lead I, should be verified in other leads. The possibility of a pseudosinus block caused by blocked premature beats which frequently are not reflected in Lead I should be excluded.

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THE ANOMALOUS MOTION OF THE HEART BORDER IN SUBJECTS WITH GALLOP RHYTHM OR THIRD HEART SOUNDS

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SLIT kymograms and electrokymograms show that most normal adults have a smooth rapid outward motion of the ventricular border of the heart in early diastole, and the tracings of the apex beat show a similar form. Lewis[1] had reported inflections on the apex tracings occurring synchronously with gallop, and Lewis and Dock[2] observed such inflections associated with the third sound in young adults. In 1946, it was noted that slit kymograms of a number of patients with gallop rhythm at Kings County Hospital showed sharp and rather deep inflections in the wave of diastolic filling at several points along the left ventricular border. This led us to undertake a systematic study of this phenomenon, in the hope that it might lead to a better understanding of the mechanism of apical diastolic sounds.

Our material came from two sources. To study the normal third sound we screened 500 healthy male high school students and chose twenty with the most typical third sounds as recorded by stethographic tracings. Our subjects with gallop rhythm were obtained from the wards of the Kings County Hospital, Long Island College Division. Among these were twenty-eight patients with protodiastolic gallop and seven with presystolic gallop. Sounds were recorded and electrokymographic studies were made only in the supine position as it has been shown that in this position the gallop and third sound are most readily heard. Border motion for fifteen patients with gallop rhythm was also recorded in the erect position with the slit kymogram. The effect of exercise and the Valsalva experiment on the slit kymograms were also studied in five normal control subjects. Ballistocardiograms were recorded in representative subjects. Simultaneous records of sounds, apical impulses, and electrocardiograms were made in combination permitting correlation of the recorded phenomena. Corrections were made for instrumental lag, which was less than 0.001 of a second for the sound and electrocardiograph and 0.035 second for the electrokymograph.

RESULTS

In every instance of protodiastolic gallop and third heart sound there was a double apical thrust in diastole, the inflection between them beginning with or slightly after the third or gallop sound. In all subjects the physiological third sound occurred in protodiastole. In patients with presystolic gallop rhythm, inflection of the apical thrust occurred in presystole about the time when pressure in the auricle begins to fall (0.11 to 0.16 second after the P wave).

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In the twenty control subjects with third sounds, the apical thrust showed protodiastolic inflection in all, while electrokymograms showed such inflections in seventeen. In fourteen of these the inflections were more marked in electrokymograms from the apex than in those from the base (Fig. 1); in three the greatest inflection was at the base (Fig. 2). The inflection occurred progressively later in diastole as the tracings were recorded from apex to base only in three subjects. The highest and latest inflection coincided with the third sound in these three cases; in others it tended to occur just before the third sound, and it usually preceded the inflection recorded in the tracings of the apex thrust.

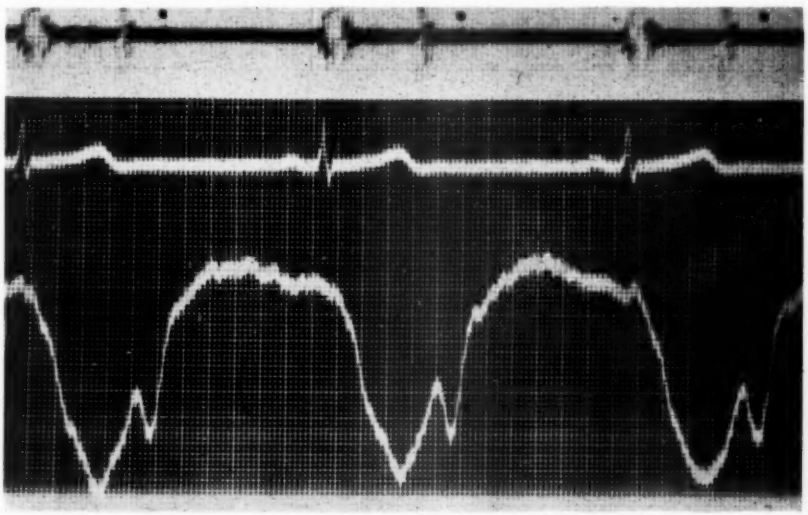

Fig. 1.—Heart sounds, electrocardiogram, and electrokymogram from a young man with third heart sounds (marked with dots). The apical part of the heart moves laterally *before* the second sound, and the inflection occurs sharply prior to the third sound in the beginning of diastole.

Of twenty patients with gallop studied with the electrokymograph, only eight showed inflections on the curve of diastolic fillings (Figs. 3 and 4); of fifteen patients studied with the slit kymograph, in the erect posture, fourteen showed inflections. In five control subjects subjected to stress of exercise or the Valsalva experiment, inflections, absent under basal conditions, were recorded by slit kymography (Fig. 5). It should be noted, however, that in eight cases, because of lack of cooperation by sick patients, the electrokymographic records were quite unsatisfactory; of the twelve with good tracings eight showed the inflections. Incidentally, others have recorded the occurrence of diastolic inflection in electrokymograms of patients with gallop, but not mentioned it in their paper (Sussman and associates[3], Fig. 1, upper left tracing).

In normal control subjects large, sharp, paradoxical lateral motions were usually recorded from the extreme apex of the left ventricle during early systole; these correspond with the apex thrust. No such inflections were recorded from the mid-ventricle or the base of the left ventricle. In deep inspiration and in the left anterior-oblique position this thrust could be recorded in an accentuated

form. In five of the twenty control subjects with third sounds we found medial motion of the base of the left ventricle continuing into early diastole. At the apex of the left ventricle lateral motion began before the second sound in ten subjects, while lateral motion at the base of the left ventricle preceded the second sound in eleven subjects. In no instance of physiological third sound did the ballistocardiogram show abnormalities of any sort, and no large wave in diastole

Fig. 2.—Electrocardiogram, heart sounds, shown by blocks, basal, mid-ventricular and apical electrokymograms, and apical thrust from the curves inscribed by a young man with third heart sounds. The inflection is deeper and later in diastole at the base of the heart.

could be correlated with the extra sound. In some instances of gallop rhythm there appeared a marked wave in diastole coinciding with the gallop sound. This was a footward movement of the body, an M wave, equal in amplitude to any wave produced in systole. This was especially noticed in those cases of gallop rhythm manifesting high cardiac output. Other tracings of gallop rhythm merely showed notched or bizarre waves in systole, often with extreme respiratory variation in size and shape.

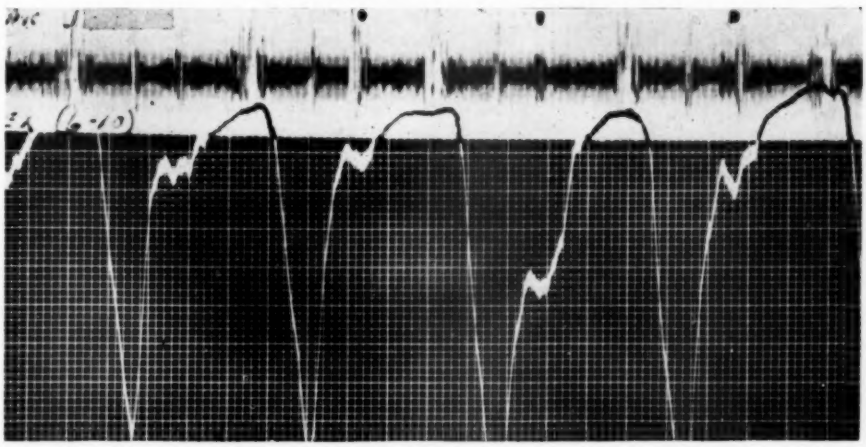

Fig. 3.—Heart sounds and electrokymogram from an elderly hypertensive patient with congestive failure. The inflection at the apex occurs just before the gallop, which, like the first sound, is followed by a short murmur. Dots mark the gallop.

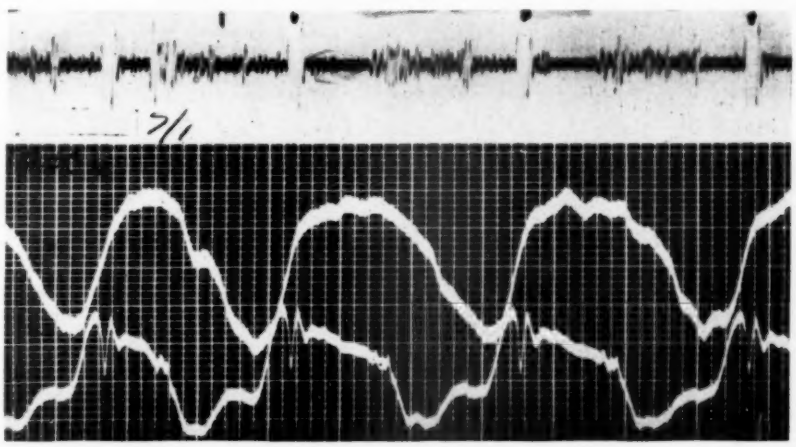

Fig. 4.—Heart sounds, electrokymogram, and apex impulse from a young woman with mitral stenosis, and patent interauricular septum. Third sound is more intense than first or second, is synchronous with the change in slope of the filling curve and the sharp, deep inflection on the apical tracing.

DISCUSSION

The term gallop rhythm was introduced by Bouillaud. However, it remained for Potain[4] to attempt an explanation for the occurrence of this extra sound. He felt that the gallop sound was due to the beginning of a sudden tension in the ventricular wall caused by the rapid flow of blood into the ventricle in diastole. He postulated that the gallop sound could originate in all cases where the elastic resistance of the wall encroached on its muscular tonicity. This could occur either by decreasing the muscular tonicity or increasing elastic resistance.

Since that time there has been much controversy over the mechanism causing the gallop sound. In a general way two schools of thought have arisen which we have arbitrarily divided into valvular and muscular. The valvular school is represented by Gibson,[5] Thayer,[6] Hirschfelder,[7] and Lewis and Dock[2]. These investigators believe the third sound is caused by the sudden closing of the auriculoventricular valves after a period of rapid diastolic filling when the in-rushing blood bounces back from the ventricle and momentarily snaps the valve taut. The muscular group is represented by Potain,[4] Ohm,[8] Wolferth and Margolies,[9] Orias and Braun-Menendez,[10] and Mannheimer.[11] It has also been suggested that the gallop sound is caused by the heart striking the chest wall and setting up an audible vibration.[12]

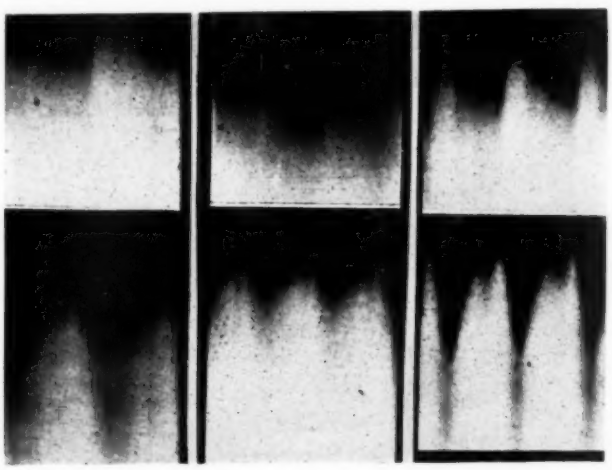

Fig. 5.—Aortic knob above, and apical ventricular border, below, recorded by slit kymograph from a young man. Left shows normal basal state; middle, with protodiastolic and presystolic inflections, after end of Valsalva experiment; right, one deep middiastolic inflection after vigorous exercise, with large stroke volume.

Inflections on diastolic filling curves of the left ventricle were noted in 1934 by Bengt-Ihre.[13] Hirsch[14] thought these occurred with the incisura on the aortic pressure wave and with the first sound. About this time King and McEachern[15] and Lewis[1] reported on the double apical impulse in gallop rhythm. In 1938, Lewis and Dock[2] proposed a theory on third heart sounds and gallop based on the idea that a reflux takes place toward the auricles at the end of rapid filling of the ventricle. The change in the shape of the ventricle with "rounding out" was stressed. Recently Cournand and his co-workers[16] recorded a sudden rise and slight fall in pressure in the right ventricle during protodiastole, together with a fall and rise in right auricular pressure. This was most striking in tricuspid insufficiency. These observations strengthened the probability that the third and gallop sounds were due to a reflux from the ventricle in early diastole, although none of the catheter studies has revealed a reversal in pressure gradient between auricle and ventricle in association with gallop. The phenomenon noted by Rytand[17]—diastolic murmurs following gallop in cases of heart block

with a systolic murmur after the first sound—which was recorded for one of our patients with normal conduction (Fig. 3) also gives strength to the thesis that reflux causes third sounds and gallop.

In 1926, Chamberlain and Dock[18] studied the action of the heart of one subject with the roentgen cinematograph. Their studies indicated that the upper ventricular border moved medially while the apex moved laterally in early diastole. A partial explanation offered was that the blood streaming along the long axis of the heart might push out the apex and cause a narrowing of the upper part of the ventricle. We found this phenomenon in only five of the twenty subjects with third sound we studied. When this is present, one could postulate taughtening of the chordae tendinae by a longitudinal stretch of the heart. In all other cases, reflux seems more probable. However, in only three of the twenty subjects was there evidence of this in the progressive movement of the inflection wave from apex to base. It seems that further light can be obtained only by catheter studies of auricular and ventricular pressures in patients with gallop which originates in the side of the heart where the catheter can penetrate.

Of practical importance is the fact that slit kymography, even in the erect position, seems to detect the diastolic inflections coincident with gallop even more regularly than the electrokymographic tracings, and that, in patients with faint heart sounds, these inflections may serve to bring to light inaudible gallop.

CONCLUSIONS

1. Our records do not prove conclusively that protodiastolic sounds are due to a reflux wave closing the auriculoventricular valves momentarily. However, such an explanation would fit exactly the phenomena we recorded in three instances where a wave of medial movement in early diastole passed from apex to base.

2. Our sound tracings do not allow of a differentiation between protodiastolic gallop and physiological third sound although Mannheimer[11] has attempted to make this differentiation using calibrated phonocardiography.

3. The fact that the apical impulse tracings showed diastolic lateral motion momentarily reversed in every instance of a third sound and protodiastolic gallop sound indicates that this sound is invariably accompanied by auricle-ward ventricular border movement in diastole. It also indicates that this is probably the most consistent and accurate method of recording cardiac motion in those who exhibit the extra sound. Almost as accurate and consistent is the slit kymogram which showed this motion in fourteen out of fifteen subjects studied. In our electrokymographic tracings only 75 per cent of those with gallop showed real inflections.

4. The ballistocardiogram showed that in some patients with gallop rhythm violent movement of blood takes place in diastole with a velocity great enough to impart more motion to the body than occurs during systole. It is conceivable that such movement of blood in diastole could cause the mitral valves to be snapped shut temporarily by its reflux from the ventricle.

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ELECTROKYMOGRAPHIC STUDIES OF THE RELATIONSHIP BETWEEN ELECTRICAL AND MECHANICAL ASYNCHRONISM IN THE CARDIAC CYCLE

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STUDIES of possible correlation between the electrical and mechanical events of the cardiac cycle have long been of interest. The initial modern studies were done by Wiggers[1,2] and Lewis,[3] although earlier work had already been recorded[4-6] on mechanical ventricular asynchronism. The work done by Wiggers and Lewis concerned, in the main, the relations between the electrocardiogram and such variables as heart sounds, peripheral arterial and venous pulse curves, and intracardiac pressure curves in animals, and laid the foundations for subsequent studies, but little work was done bearing more directly on the relationship between the asynchronism of mechanical ejection from the ventricles and electrical asynchronism as revealed by electrocardiograms showing bundle branch block. Stassen[4] and Fauconnier[5] studied ventricular pulsations in animals by means of a myocardiograph and found that the right ventricle normally started to contract before the left. Eppinger and Rothberger[6] measured ventricular asynchronism by recording the onsets of aortic and pulmonic pulsations in animals with a solenoid recorder. They found a normal asynchronism of 0.01 second, with either side ahead in different experiments.

Katz[7] recorded right and left ventricular as well as pulmonary artery and aortic pressures in dog experiments. He found that mechanical asynchronism of the two ventricles existed in that neither the onset of isometric contraction nor the beginning of ejection nor the end of systole was synchronous in the two ventricles. The right ventricular ejection was ahead of the left by 0.011 to 0.027 second in eleven animals. In a like number, left ventricular ejection preceded right ventricular ejection by 0.013 to 0.030 second. In two experiments ejection started simultaneously on the two sides. Katz felt that the asynchronous onset of right and left ventricular ejection was due "to differences in the interval elapsing between excitation and contraction of a sufficient number of muscle elements to elevate the initial pressure in the two ventricles." He also felt that differences in the initial tension of ventricular fibers and differences in aortic and pulmonary resistances could give rise to a state of asynchronism of the two ventricles. No evidence was presented to suggest that electrical asynchronism

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was responsible for mechanical asynchronism. Wiggers and Banus[8] studied electrical and mechanical phenomena in the mammalian ventricles and concluded that the two are independent in that variations in the two phenomena are not necessarily correlated.

Clinical studies attempting to show mechanical ventricular asynchronism in the presence of electrical asynchronism have met with only partial success. Wolferth and Margolies[9,10] studied eleven cases of left bundle branch block, measuring the interval from the onset of the QRS to the beginning of the right carotid artery pulsation in the neck. In normals this interval ranged from 0.09 to 0.15 second, with an average value of 0.11 second. In eleven cases of left bundle branch block, the range was 0.16 to 0.21 second, average 0.17 second. In one case multiple ventricular premature contractions were noted. When the QRS complex was downward in Lead I (suggesting a left ventricular premature beat), the QRS to carotid interval was 0.13 second, but when the QRS was upright in Lead I (suggesting a right ventricular premature), the interval was 0.20 second. From these results the authors concluded that correlation between the electrical and mechanical phases of the cardiac cycle did occur. Nichol[11] came to the same conclusion as a result of a similar study. However, Katz[12] has criticized the work of Wolferth and Margolies, and Nichol. He employed the same techniques but, unlike the others, he failed to find that the pulse wave arrived later than normally in the carotid artery in most cases of left bundle branch block. Battro[13] came to the conclusion that "the electrocardiogram by itself is not a reliable means for establishing the diagnosis of complete bundle branch block with its mechanical consequences" in a study of twenty cases of bundle branch block after recording the apex beat, central arterial and venous pulses, heart sounds, and the electrocardiogram. He went on to state that "it is the adequate recording of mechanical events due to the heart action which affords the only means to determine the existence of ventricular asynchronism."

On the other hand, Castex and co-workers[14] found that they could correlate the site of origin of ventricular premature beats with the interval from the onset of the QRS complex to the onset of the carotid artery pulse with some success. In ten cases, when the QRS complex of a ventricular premature complex was downward in Lead I (therefore, a left ventricular premature beat), the QRS-carotid interval ranged from 0.11 to 0.22 second, average 0.17 second. In thirteen cases when the QRS complex of a ventricular premature beat was upward in Lead I (therefore, a right ventricular premature beat), the QRS-carotid interval ranged from 0.16 to 0.28 second, average 0.22 second. Kossman and Goldberg[15] published the results of QRS onset to onset of carotid pulsation intervals in eight normals (range 0.131 to 0.148 second, average 0.139 second), in three patients with complete left bundle branch block (range 0.195 to 0.233 second, average 0.213 second), and five patients with complete right bundle branch block (range 0.120 to 0.180 second, average 0.151 second), and concluded that mechanical ventricular asynchronism had been demonstrated. Richards and co-workers[16,17] measured the interval between the onset of the QRS and onset of isometric contraction in the right ventricle (with an intracardiac catheter) and between the onset of the QRS and onset of pressure rise in the brachial artery (with an indwelling

needle) in normals, patients with bundle branch block, and patients with ventricular premature beats. In three cases of left bundle branch block, they noted evidence of delayed mechanical ejection from the left side of the heart as evidenced by a prolonged interval between the onset of the QRS and the onset of the brachial artery pressure rise. The QRS to onset of right ventricular isometric contraction interval was normal. In five cases of right bundle branch block, the QRS to right ventricular isometric contraction interval was prolonged but the QRS to brachial interval was also prolonged in some instances. From this data the authors concluded that ventricular asynchronism occurred in bundle branch block. However, when the mechanical events accompanying ventricular premature beats were studied, it was found that "it is difficult to interpret the relationship between the electrical configuration of premature contractions and the mechanical events, since different electrical patterns give the same type of ventricular asynchronism." The data of the last three groups of investigators cannot be questioned, but we feel that the interpretations deduced from these results can be questioned for reasons to be discussed later.

With the development of the electrokymogram,[18-21] a new technique has become available for study of the problem of whether or not correlation of electrical and mechanical events of the cardiac cycle does occur. We specifically became interested in determining whether or not electrical asynchronism of the ventricles (as noted in bundle branch block, complete heart block with idioventricular rhythm, and ventricular premature contractions) could be correlated with mechanical ventricular asynchronism. Ellinger and associates[24] have already published a study of ascending aorta and pulmonary artery electrokymograms in sixteen cases of bundle branch block. Tracings of the ascending aorta and pulmonary artery were recorded, not simultaneously with each other, but simultaneously with a carotid artery pulse tracing, and comparison of the electrokymograms of the two great vessels was made indirectly by using the carotid artery pulse curve as a reference point. Their results indicated that left bundle branch block was associated with delayed mechanical ejection from the left ventricle and right bundle branch block with delayed ejection from the right ventricle, when compared to the time relations of ascending aorta and pulmonary artery electrokymograms in normals. These investigators thus felt that electrical asynchronism was accompanied by mechanical asynchronism of ventricular ejection. However, only sixteen cases were studied.

We have studied this same problem in eighty-three patients with bundle branch block, two patients with complete heart block with idioventricular rhythm, and twenty-one ventricular premature beats in fourteen patients by the technique of simultaneous electrokymography. In all cases the diagnosis of bundle branch block was made from three standard and six unipolar precordial leads, using the site of the delayed intrinsicoid deflection to determine the side of the bundle branch block.

TECHNIQUE

In a study of possible correlation between electrical and mechanical ventricular asynchronism, recordings of the electrokymograms of the two ventricles simultaneously would have been the most desirable approach. By such tech-

nique the onset of isometric contraction and ejection from both ventricles could have been determined simultaneously[21] and the presence or absence of mechanical asynchronism in onset of both isometric contraction and ejection determined for the ventricles. However, such records, while they have been obtained in fifty-three normal individuals,[25] do not show sharply defined and measurable points of onset of isometric contraction and ejection of the two ventricles in all cases. We therefore decided to record electrokymograms of the ascending aorta and pulmonary artery simultaneously (thereby limiting ourselves to a study of asynchronism in ejection only) and have been able to record such tracings satisfactorily in every patient, normal and abnormal, that we have studied. With the patient sitting on a low stool in the right anterior oblique position, the ascending aorta and (below the ascending aorta) the pulmonary artery are readily visible on the anterior border of the heart. The photoelectric pick-up units of the electrokymographs can be placed over the border of the ascending aorta and pulmonary artery in this position so as to obtain the proper tracings. The fluoroscopic placing of the photoelectric cell was done by an experienced fluoroscopist (J. B. S.) in all patients. Comparison of the time relation between the onset of left ventricular ejection (on the ascending aorta electrokymogram) and right ventricular ejection (by the pulmonary artery electrokymogram) can thus be made readily and rapidly without recourse to any reference points. More accurate measurements are therefore possible. Lead I of the electrocardiogram was recorded simultaneously with the two electrokymograms on a three-beam direct-writing Technicon* in order to allow a simultaneous study of the interval between onset of electrical ventricular depolarization and mechanical ventricular ejection. The use of a direct writing apparatus permits immediate repetition of any tracings showing a slurred onset of great vessel ejection and thus also results in more accurate measurements. On repetition our results have been found to be reproducible within the error of measurement of 0.01 second. The patients were all veterans from 25 to 75 years of age.

RESULTS

The results will be discussed with the aid of tables. Table I shows the results of recording Lead I and electrokymograms of the ascending aorta and pulmonary artery simultaneously in twenty-five young normal men. The normal relationship between the onset of pulmonary artery and ascending aorta ejection is plus 0.03 to minus 0.02 second. That is, pulmonary artery ejection may precede ascending aorta ejection by as much as 0.03 second or follow it by as much as 0.02 second. This range of normality is almost identical with that noted by Ellinger and associates[24] in sixty-eight cases. In these twenty-five normal individuals, left ventricular ejection preceded right ventricular ejection in twelve cases, right ventricular ejection preceded left in ten cases, and the two sides were simultaneous in three cases. These results are similar to those obtained by Katz[7] and Ellinger and co-workers[24] but differ somewhat from those obtained by Hamilton and associates,[26] who found the left ventricle to precede the right

*We are indebted to the Technicon Corp., 215 East 149th St., Bronx, N. Y., for the use of this instrument.

in most patients. Our over-all data in Table I show no difference in ejection from the two ventricles. The interval from the onset of the QRS to the onset of ejection in the two great vessels averages 0.118 second. In all patients except 3, 4, and 11, the QRS to ejection interval is less than 0.15 second.

TABLE I. NORMALS

CASE	NAME	RELATION PUL. A.* AND ASC. A.	QRS TO ASC. A.	QRS TO PUL. A.
1	J. C.	−0.02	0.09	0.11
2	A. C.	0.03	0.13	0.10
3	K. J.	0.01	0.16	0.15
4	J. M.	−0.02	0.15	0.17
5	W. S.	0.03	0.11	0.08
6	W. F.	−0.02	0.13	0.15
7	B. S.	−0.02	0.12	0.14
8	U. P.	0.02	0.13	0.11
9	C. R.	−0.02	0.11	0.13
10	R. D.	0.00	0.12	0.12
11	R. S.	−0.02	0.14	0.16
12	S. B.	0.02	0.14	0.12
13	W. S.	−0.01	0.10	0.11
14	J. D.	−0.02	0.09	0.11
15	F. R.	0.02	0.12	0.10
16	D. F.	0.03	0.11	0.08
17	A. F.	0.01	0.10	0.09
18	E. W.	0.01	0.11	0.10
19	J. S.	−0.02	0.12	0.14
20	S. R.	0.02	0.13	0.11
21	F. P.	−0.01	0.11	0.12
22	W. S.	0.00	0.10	0.10
23	A. B.	−0.01	0.10	0.11
24	S. K.	0.00	0.13	0.13
25	J. N.	−0.01	0.11	0.12
Average		0.00	0.118	0.118

*A minus sign means the ascending aorta is ahead of the pulmonary artery.

Table II, Group A illustrates the results in twenty-seven cases of complete right bundle branch block (QRS> 0.12 second). In all the patients here, the relation between onset of pulmonary artery and ascending aorta ejection is within the normal limits given above. There is no correlation between electrical asynchronism as shown by bundle branch block and mechanical ventricular ejection asynchronism. However, study of the intervals between onset of the QRS and onset of ejection reveals significant data. In the great majority of patients the QRS ejection interval is prolonged for both ventricles. That is, there is evidence of delayed ejection from both ventricles regardless of the site of bundle branch block revealed by the electrocardiogram. The average value for QRS to ejection interval is 0.179 second on the left side and 0.178 second on the right side. One can hardly maintain that correlation of electrical and mechanical ejection asynchronism occurs in this group. Table II, Group B demonstrates the results in eleven additional cases of complete right bundle branch block. In this group the onset of ascending aorta ejection is abnormally ahead of the onset of pulmonary

artery ejection and correlation between mechanical and electrical asynchronism is apparently present. However, even in these cases there is evidence of delayed left-sided ejection (average QRS to ejection interval is 0.140 second) in many cases, despite the presence of right bundle branch block. Right ventricular ejection is uniformly delayed in these eleven cases with an average QRS to ejection time of 0.186 second.

TABLE II. COMPLETE RBBB (QRS > 0.12)

CASE	NAME	QRS	RELATION PUL. A.* AND ASC. A.	CORRELATION	QRS TO ASC. A.	QRS TO PUL. A.
			Group A			
1	J. R.	0.13	0.03	No	0.21	0.18
2	C. F.	0.13	0.00	No	0.20	0.20
3	U. N.	0.13	0.02	No	0.16	0.14
4	J. B.	0.13	−0.02	No	0.17	0.19
5	S. D.	0.13	0.00	No	0.18	0.18
6	J. F.	0.13	0.00	No	0.20	0.20
7	S. C.	0.13	0.00	No	0.16	0.16
8	J. W.	0.13	0.00	No	0.15	0.15
9	M. S.	0.13	0.01	No	0.18	0.17
10	E. S.	0.13	−0.02	No	0.15	0.17
11	M. M.	0.13	0.00	No	0.15	0.15
12	J. T.	0.13	−0.02	No	0.16	0.18
13	A. D.	0.13	0.01	No	0.17	0.16
14	J. F.	0.14	0.00	No	0.12	0.12
15	L. L.	0.14	0.01	No	0.17	0.16
16	H. A.	0.14	0.00	No	0.16	0.16
17	J. S.	0.14	0.01	No	0.17	0.16
18	J. A.	0.14	0.00	No	0.17	0.17
19	S. R.	0.15	0.00	No	0.18	0.18
20	S. A.	0.15	0.00	No	0.21	0.21
21	F. Y.	0.15	−0.01	No	0.23	0.24
22	K. L.	0.15	0.00	No	0.18	0.18
23	P. C.	0.15	−0.01	No	0.19	0.20
24	I. S.	0.15	−0.01	No	0.21	0.22
25	S. A.	0.16	0.02	No	0.22	0.20
26	M. F.	0.16	0.00	No	0.19	0.19
27	S. B.	0.16	0.00	No	0.19	0.19
Average			0.001		0.179	0.178
			Group B			
28	U. B.	0.13	−0.04	Yes	0.14	0.18
29	B. S.	0.13	−0.05	Yes	0.12	0.17
30	C. Q. L.	0.13	−0.03	Yes	0.12	0.15
31	A. R.	0.13	−0.04	Yes	0.17	0.21
32	M. D.	0.13	−0.04	Yes	0.17	0.21
33	J. T.	0.13	−0.04	Yes	0.13	0.17
34	J. G.	0.14	−0.09	Yes	0.13	0.22
35	E. B.	0.14	−0.04	Yes	0.17	0.21
36	J. B.	0.14	−0.04	Yes	0.11	0.15
37	F. S.	0.14	−0.04	Yes	0.14	0.18
38	W. C.	0.16	−0.06	Yes	0.14	0.20
Average			−0.046		0.140	0.186

*A minus sign means the ascending aorta is ahead of the pulmonary artery.

TABLE III. COMPLETE LBBB (QRS > 0.12)

CASE	NAME	QRS	RELATION PUL. A.* AND ASC. A.	CORRELATION	QRS TO ASC. A.	QRS TO PUL. A.
			Group A			
1	T. N.	0.13	−0.03	No	0.08	0.11
2	R. Q.	0.13	0.02	No	0.16	0.14
3	H. S.	0.13	0.02	No	0.18	0.16
4	J. G.	0.14	0.01	No	0.22	0.21
5	T. D.	0.14	0.02	No	0.16	0.14
6	C. B.	0.14	0.02	No	0.17	0.15
7	L. W.	0.14	0.02	No	0.12	0.10
8	R. P.	0.14	0.02	No	0.12	0.10
9	E. S.	0.14	0.03	No	0.14	0.11
10	C. B.	0.15	0.02	No	0.14	0.12
11	M. R.	0.16	0.01	No	0.17	0.16
Average			0.014		0.151	0.136
			Group B			
12	A. M.	0.13	0.06	Yes	0.19	0.13
13	J. B.	0.13	0.07	Yes	0.15	0.08
14	S. K.	0.13	0.07	Yes	0.19	0.12
15	N. A.	0.13	0.04	Yes	0.16	0.12
16	D. R.	0.14	0.05	Yes	0.17	0.12
17	D. R.	0.14	0.07	Yes	0.21	0.14
18	S. K.	0.14	0.18?	Yes	0.21	0.03?
19	A. B.	0.15	0.08	Yes	0.20	0.12
20	C. O.	0.15	0.04	Yes	0.16	0.12
21	J. D.	0.15	0.04	Yes	0.14	0.10
22	A. C.	0.16	0.06	Yes	0.24	0.18
23	C. F.	0.18	0.04	Yes	0.19	0.15
Average			0.075		0.184	0.117

*A minus sign means the ascending aorta is ahead of the pulmonary artery.

Table III shows our results in twenty-three cases of complete left bundle branch block. In Group A the relation between the onset of pulmonary artery and ascending aorta ejection is within normal limits. However, there is evidence of delayed mechanical ejection from both sides of the heart in the over-all data. On the left side the QRS to ejection interval is 0.151 second, while on the right it is 0.136 second. These figures indicate that left ventricular ejection is delayed more than right ventricular ejection. Several cases demonstrate a normal QRS to ejection interval from both sides of the heart. Special attention should be drawn to Case 1 of Group A. Despite the presence of left bundle branch block, the onset of ascending aorta ejection is abnormally ahead of the onset of pulmonary artery ejection. In this case there is an abnormal relation between pulmonary artery and ascending aorta upstrokes, but in a direction opposite to that expected were correlation between electrical and mechanical ejection asynchronism uniformly present. In the last twelve cases of Table III there is evidence of marked ejection asynchronism, with one difference of 0.18 second in

onset of ejection from the two sides. We have questioned the results in that case (S. K.) because of the great time difference in ejection from the two sides of the heart. In this Group B there is fairly uniform evidence of delayed left ventricular ejection, but except for isolated cases (especially Cases 22 and 23, A. C., and C. F.), there is little evidence of delayed mechanical ejection from the right side. In Group B the average QRS to ejection intervals are 0.184 and 0.117 second for the left and right ventricles, respectively. It is interesting that fully one-half of the cases of complete left bundle branch block showed apparent correlation between electrical and ejection asynchronism, while only about 25 per cent of the cases of complete right bundle branch block showed such correlation.

TABLE IV. INCOMPLETE RBBB (QRS 0.11 OR 0.12)

CASE	NAME	QRS	RELATION PUL. A.* AND ASC. A.	CORRELATION	QRS TO ASC. A.	QRS TO PUL. A.
			Group A			
1	W. T.	0.11	0.04	No	0.16	0.12
2	R. F.	0.11	0.03	No	0.16	0.13
3	H. S.	0.11	0.00	No	0.16	0.16
4	N. R.	0.12	0.02	No	0.18	0.16
5	M. W.	0.12	0.05	No	0.16	0.11
6	M. C.	0.12	−0.02	No	0.16	0.18
7	V. S.	0.12	−0.01	No	0.18	0.19
8	I. B.	0.12	−0.01	No	0.20	0.21
9	D. D.	0.12	0.00	No	0.16	0.16
10	J. M.	0.12	0.01	No	0.18	0.17
Average			0.011		0.170	0.159
			Group B			
11	M. F.	0.11	−0.06	Yes	0.12	0.18
12	S. C.	0.12	−0.03	Yes	0.12	0.15
13	J. I.	0.12	−0.06	Yes	0.14	0.20
Average			−0.050		0.126	0.176

*A minus sign means the ascending aorta is ahead of the pulmonary artery.

Table IV illustrates our results in thirteen cases of incomplete right bundle branch block. Eight cases of Group A show a normal relation between onset of pulmonary artery and ascending aorta ejection. Special attention should be drawn to Cases 1 and 5. Despite the presence of incomplete right bundle branch block, the onset of pulmonary artery ejection is abnormally ahead of the onset of ascending aorta ejection. There is an abnormal relation between the two great vessels here, but it is in a direction opposite to that expected were it always possible to correlate electrical and mechanical ventricular ejection asynchronism. Note, however, that there is again evidence of delayed ejection from both sides of the heart despite the electrocardiographic pattern of delay only in right ventricular depolarization. The average values for QRS to ejection

intervals are 0.17 second for the left ventricle and 0.159 second for the right ventricle. In Group B, the abnormal relation between onset of ejection from the two great vessels is in a direction expected for the type of bundle branch block. There is evidence of uniform delay in right ventricular ejection in this group (QRS to ejection time of 0.176 second) but little, if any, evidence of delay in left ventricular ejection (QRS to ejection time of 0.126 second).

TABLE V. INCOMPLETE LBBB (QRS 0.11 OR 0.12)

CASE	NAME	QRS	RELATION PUL. A.* AND ASC. A.	CORRELATION	QRS TO ASC. A.	QRS TO PUL. A.
			Group A			
1	M. M.	0.12	0.03	No	0.19	0.16
2	A. S.	0.12	0.02	No	0.14	0.12
3	J. S.	0.12	0.02	No	0.12	0.10
4	M. R.	0.12	0.02	No	0.14	0.12
5	J. K.	0.12	0.03	No	0.16	0.13
6	A. S.	0.12	0.01	No	0.14	0.13
7	E. C.	0.12	0.02	No	0.14	0.12
Average			0.021		0.150	0.125
			Group B			
8	S. H.	0.11	0.05	Yes	0.12	0.07
9	O. S.	0.12	0.08	Yes	0.20	0.12
Average			0.065		0.16	0.095

*A minus sign means the ascending aorta is ahead of the pulmonary artery.

Table V illustrates our results in nine cases of incomplete left bundle branch block. In Group A all seven show a normal relation between onset of ejection from the two ventricles. There is minimal evidence of delayed right ventricular ejection (QRS to ejection interval average 0.125 second) but evidence of delayed left ventricular ejection (QRS to ejection interval of 0.150 second). In Group B the relation between onset of ejection from the two ventricles is abnormal in a direction to be expected. Right-sided ejection time is normal (QRS to ejection interval 0.095 second), but left-sided ejection is delayed (QRS to ejection interval 0.16 second).

TABLE VI. COMPLETE HEART BLOCK

CASE	NAME	QRS	RELATION PUL. A.* AND ASC. A.	CORRELATION	QRS TO ASC. A.	QRS TO PUL. A.
1	H. S.	0.14 (R. V. focus)	0.02	No	0.14	0.12
2	F. L.	0.11 (L. V. focus)	−0.06	Yes	0.11	0.17

*A minus sign means the ascending aorta is ahead of the pulmonary artery.

Table VI demonstrates two cases of complete heart block with idioventricular rhythm. H. S., with a right ventricular focus (and, therefore, the pattern of left bundle branch block on the electrocardiogram) shows a normal relation between ejection on the two great vessels, with no evidence of delayed mechanical ejection from either side of the heart. F. L. (2), with a left ventricular focus (and, therefore, the pattern of right bundle branch block on the electrocardiogram) demonstrates that the onset of left ventricular ejection is abnormally ahead of the onset of right ventricular ejection. Delayed mechanical ejection is present from the right ventricle only in this case.

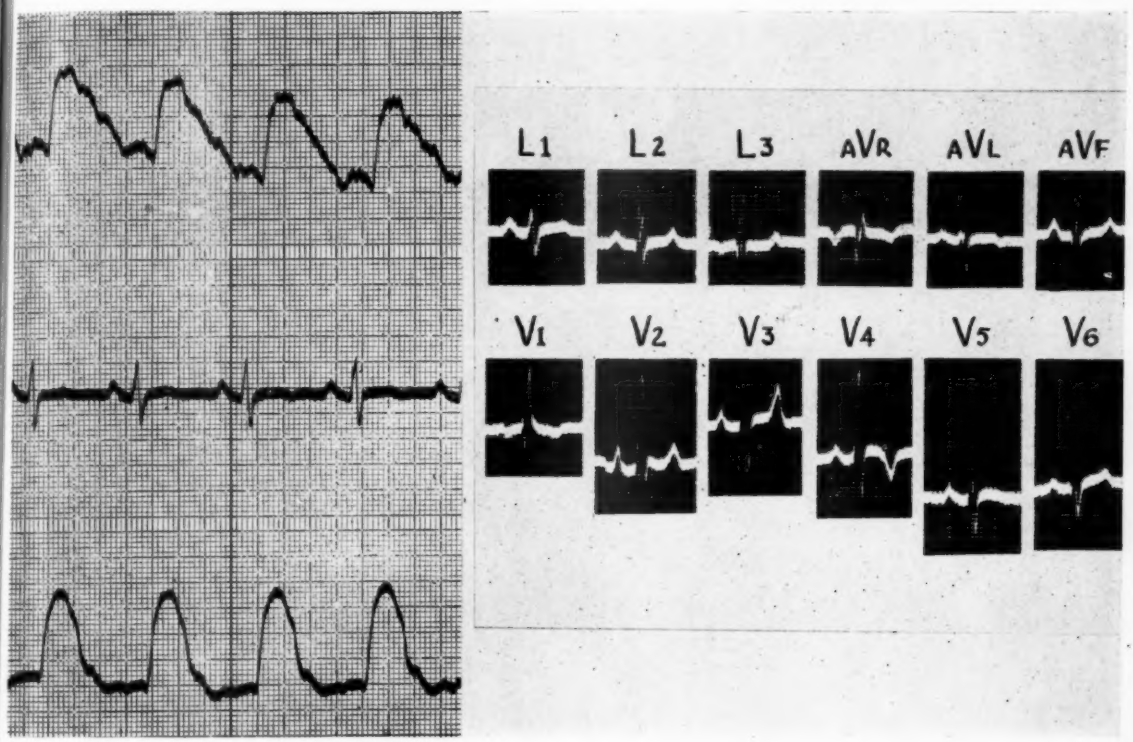
TABLE VII. VENTRICULAR PREMATURE BEATS

CASE	NAME	V.P.C.	QRS	RELATION PUL. A.* AND ASC. A.	CORRELATION	QRS TO ASC. A.	QRS TO PUL. A.
1	J. F.	L	0.14	0.00	No	0.26	0.26
		R	0.14	0.00	No	0.26	0.26
2	O. S.	L	0.12	0.03	Yes		
3	A. P.	L	0.13	−0.08	Yes	0.20	0.28
4	F. B.	L	0.13	−0.03	Yes	0.15	0.18
		L	0.13	0.00	No	0.20	0.20
5	T. D.	L	0.14	0.02	No	0.22	0.20
6	I. N.	R	0.13	0.04	Yes		
		R	0.13	0.00	No	0.20	0.20
		R	0.14	−0.02	No		
7	C. C.	L	0.15	0.01	No	0.20	0.19
8	N. A.	R	0.14	0.04	Yes	0.19	0.15
		R	0.14	−0.04	No	0.14	0.18
9	I. L.	L	0.14	−0.01	No	0.13	0.14
		L	0.14	0.00	No	0.13	0.13
10	W. C.	R	0.11	0.00	No	0.12	0.12
		L	0.12	0.01	No	0.13	0.12
11	J. D.	R	0.14	0.00	No	0.16	0.16
12	A. N.	R	0.14	0.02	No	0.18	0.16
13	E. S.	L	0.16	0.00	No	0.10	0.10
14	A. D.	R	0.12	0.05	Yes	0.20	0.15

*A minus sign means the ascending aorta is ahead of the pulmonary artery.

Table VII shows our results in twenty-one ventricular premature contractions in fourteen patients. In only six premature beats is the relation between the onset of ascending aorta and pulmonary artery ejection abnormal. In the remaining fifteen the relationship is within normal limits. However, in more than one-half of these ventricular premature contractions there is evidence of delayed mechanical ejection from both sides of the heart regardless of the site of origin of the premature beat as shown on Lead I of the electrocardiogram. Correlation of mechanical ejection asynchronism with the absence or presence of a delayed ejection time does not occur in this group of cases. In Case 8, N. A., note that in a right ventricular premature beat the relation is minus 0.04 second. The onset of left ventricular ejection is abnormally ahead of the onset of right ventricular ejection despite the origin of the premature beat in the right ventricle. In some instances because of uncertainty in measuring the exact onset of the QRS complex, it was not possible to measure the QRS to ejection interval.

From the over-all results it is again not possible to correlate electrical and mechanical ejection asynchronism. Figs. 1 to 6 show representative curves illustrating the points made above.



A. B.

Fig. 1.—Illustrating the curves obtained in W. T., a patient with incomplete right bundle branch block with a QRS complex of 0.11 second (Table IV, Case 1).

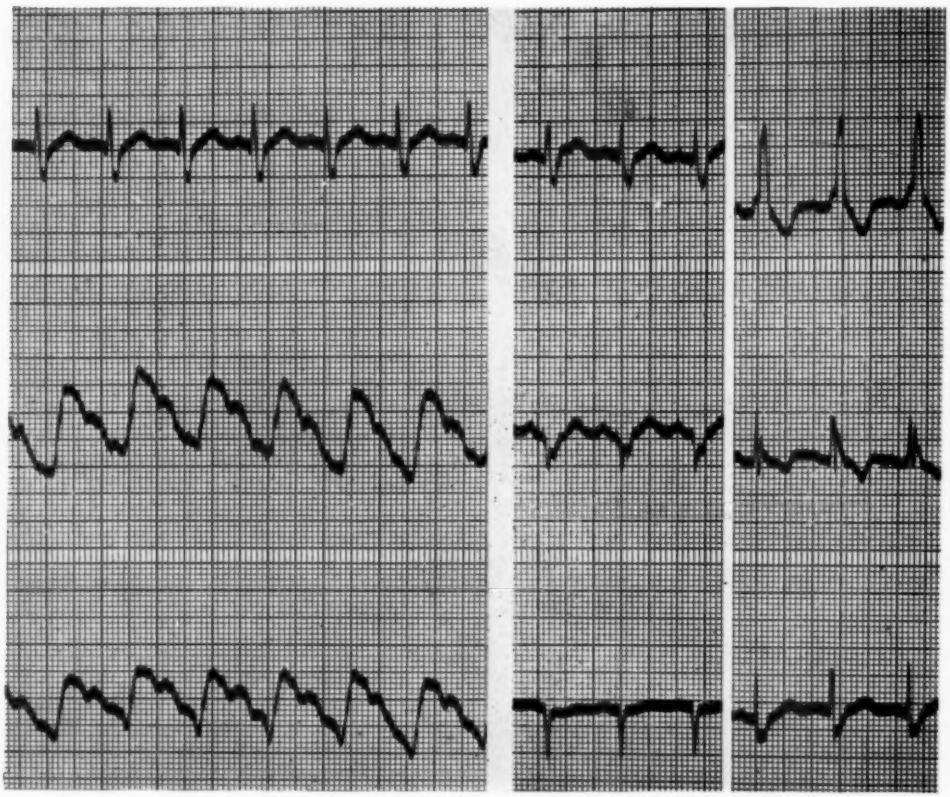
A, The electrokymogram of the ascending aorta, Lead I of the electrocardiogram, and the electrokymogram of the pulmonary artery are shown from above down. The upstroke of the pulmonary artery —onset of right ventricular ejection—is 0.04 to 0.05 second ahead of the upstroke of the ascending aorta electrokymogram. Despite the presence of incomplete right bundle branch block, the onset of right ventricular ejection is abnormally ahead of the onset of left ventricular ejection. The QRS ejection interval is prolonged for the left side of the heart only.

B, The electrocardiogram, demonstrating right bundle branch block, with a delayed intrinsicoid deflection in V_1 and V_2.

DISCUSSION

Our over-all results have demonstrated the lack of correlation between electrical and mechanical ejection asynchronism in fifty-five of the eighty-three cases of bundle branch block. Only one of two cases of complete heart block with idioventricular rhythm showed mechanical asynchronism and but six of twenty-one ventricular premature beats showed ejection asynchronism. With these results in mind we at first tended to state simply that one could not correlate electrical and mechanical asynchronism of the ventricles in the cardiac cycle and let it go at that. However, closer perusal of the onset of the QRS to onset of

ejection intervals for both sides of the heart led us to the realization that we were perhaps missing the fundamental issue here. The absence or presence of mechanical ejection asynchronism is of relatively little fundamental importance. The basic point is that mechanical ejection is delayed from both sides of the heart in the majority of bundle branch block cases, irrespective of the side of the bundle branch block, especially when ventricular ejection asynchronism is absent. Whether or not ejection asynchronism is present depends on the relative degree of delay of ejection from the right and left ventricles. The onset of the



A. B.

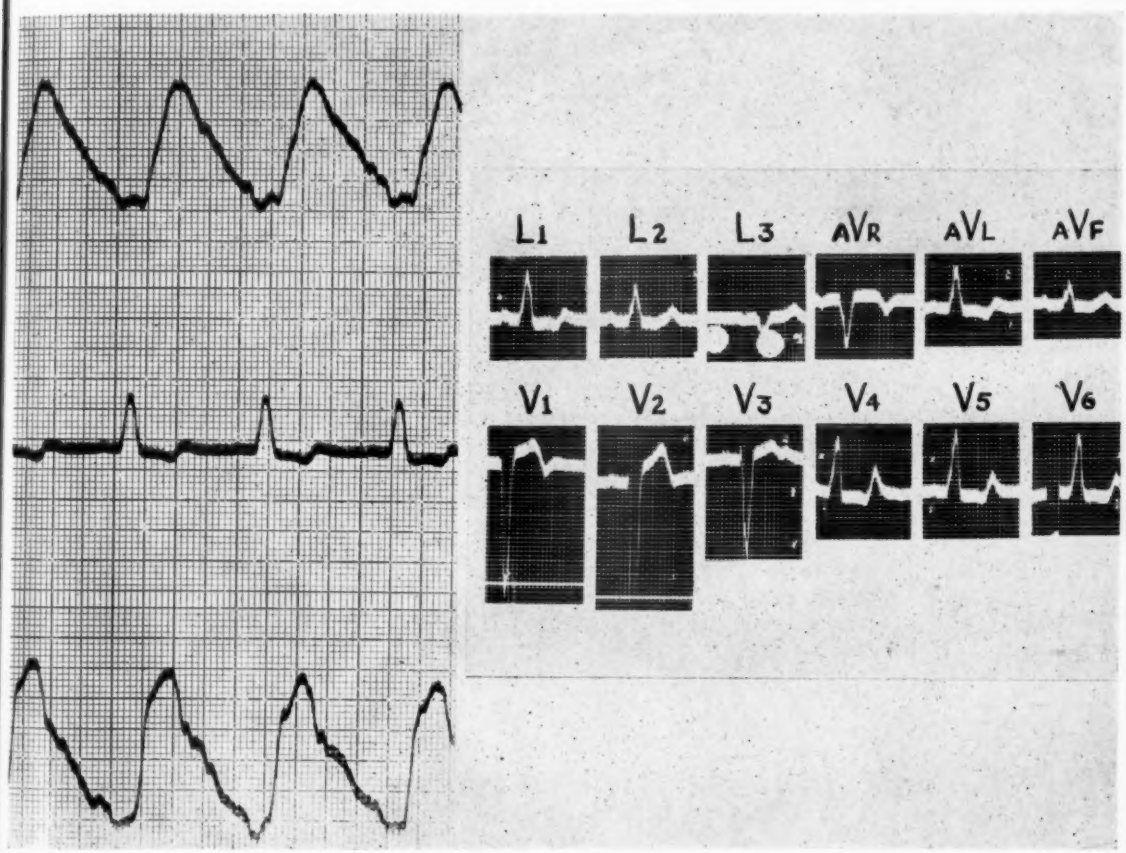
Fig. 2.—Showing the results obtained in J. W., a patient with complete right bundle branch block, QRS 0.13 second (Table II, Group A, Case 8).

A, Lead I, and the electrokymograms of the ascending aorta and pulmonary artery, respectively, are shown from above down. The onset of ventricular ejection is simultaneous on the two sides. However, there is some evidence of delayed ejection from both sides of the heart as noted by a QRS to ejection interval of 0.15 second bilaterally.

B, Leads I, II and II taken simultaneously are shown to the left from above down. To the right from above down, V_1, V_2, and V_5 are shown.

QRS to onset of ejection interval is the basic independent measurement which in turn determines the presence or absence of mechanical ejection asynchronism. There is, however, a tendency for the QRS to ejection figures on the side opposite to the block to be more normal in those cases of bundle branch block where

there is mechanical asynchronism than in those cases where ejection asynchronism is absent. Case 1 of Table III, Cases 1 and 5 of Table IV, and Case 8 of Table VII all demonstrate the difficulties encountered in attempting to correlate electrical and mechanical phenomena of the cardiac cycle. In all four instances there is an abnormal mechanical ejection relationship between the onset of ascending aorta and pulmonary artery ejection, but in a direction opposite to that expected.



A. B.

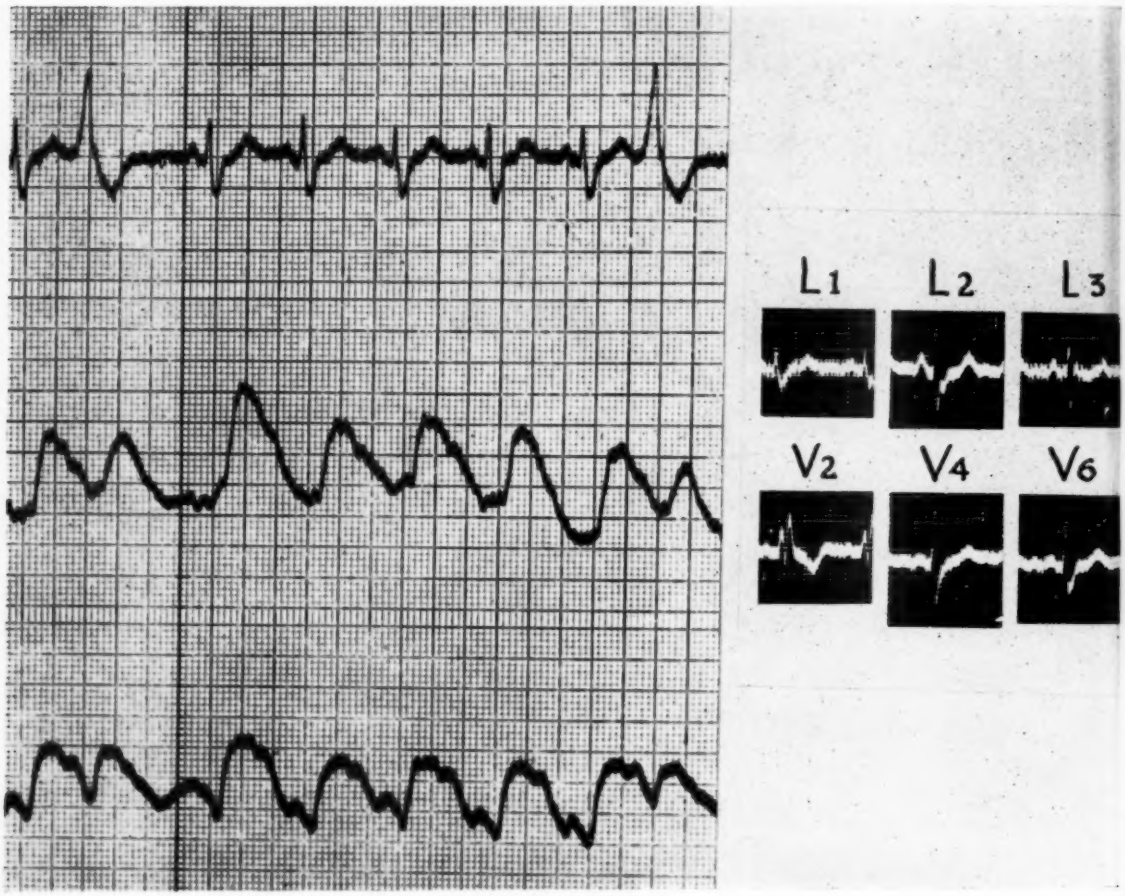
Fig. 3.—Demonstrating the tracings obtained in R. Q., a patient with complete left bundle branch block with a QRS complex of 0.13 second (Table III, Case 2).

A, The electrokymogram of the ascending aorta, Lead I, and the electrokymogram of the pulmonary artery are shown from above down. The upstroke of the pulmonary artery is 0.02 second ahead of the upstroke of the ascending aorta—a relation with normal limits. There is only minimal delay in right ventricular ejection (QRS to ejection interval of 0.14 second), but more definite evidence of delayed left ventricular ejection (QRS to ejection interval of 0.16 second).

B, The electrocardiogram shows complete left bundle branch block with a delayed intrinsicoid deflection from the left side of the heart.

With the above factors in mind, a re-evaluation of certain papers discussed above is in order. In the studies of Wolferth and Margolies[9,10] a delay in the onset of QRS to onset of carotid pulse wave was found in eleven cases of left

bundle branch block, compared to normals. But simultaneous studies of right ventricular ejection were not undertaken and the definite possibility exists that such studies would have revealed delayed right ventricular ejection. Therefore the presence of delayed ventricular ejection on one side does not permit the conclusion that mechanical asynchronism is present. Furthermore, in six cases of left bundle branch block studied by Wolferth and Margolies with roentgenkymograms of both the pulmonary artery and aortic knob, the onset of pulmonary



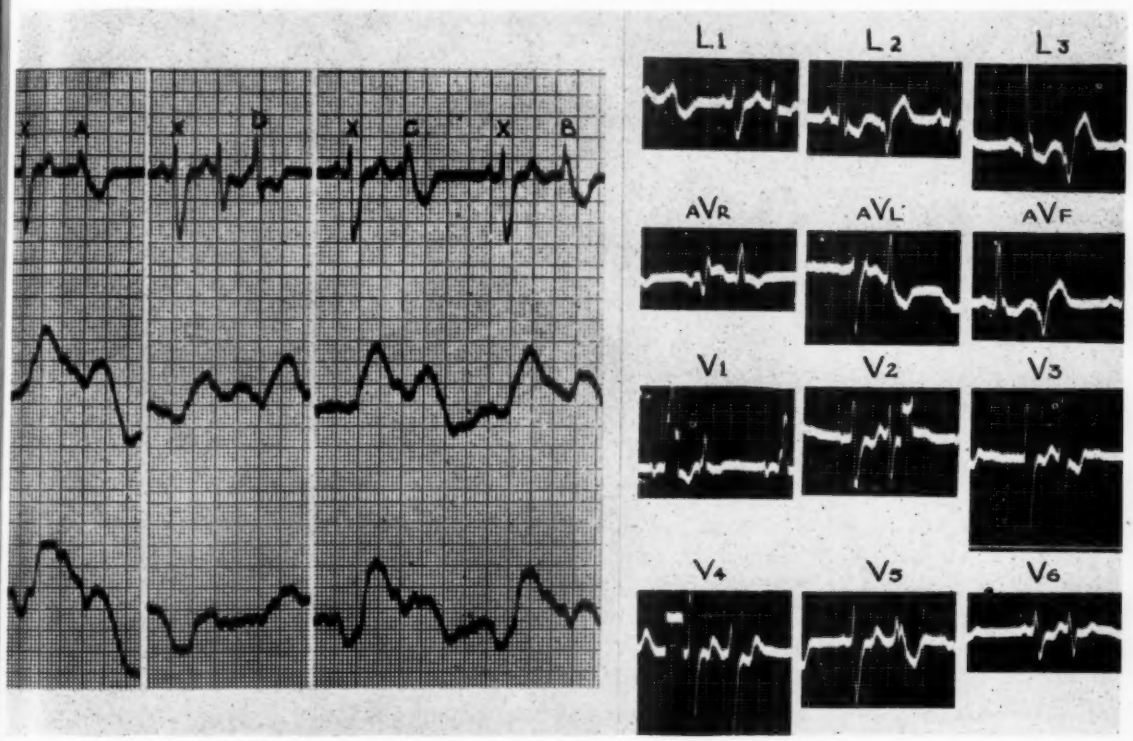
A. B.

Fig. 4.—Showing the curves obtained in A. D., a patient with complete right bundle branch block, QRS 0.13 second (Table II, Group A, Case 13) and with multiple right ventricular premature beats recorded in Lead I (Table VII, Case 14).

A, Lead I and the electrokymograms of the ascending aorta and pulmonary artery are noted from above down. The upstroke of the pulmonary artery is 0.01 second ahead of the upstroke of the ascending aorta, a relation well within normal limits. Ejection time is, however, delayed on both sides of the heart. The QRS to ejection interval on the left side is 0.17 second, and is 0.16 second on the right side. The mechanical relations of the two right ventricular premature beats are abnormal, however, in that the upstroke of the pulmonary artery is 0.05 second ahead of the upstroke of the ascending aorta. Mechanical ejection asynchronism is noted only in the premature beats. Note that left-sided ejection in the premature beats is markedly delayed, while right-sided ejection is moderately delayed.

B, The electrocardiogram showing complete right bundle branch block.

artery ejection was ahead of the corresponding phase on the aortic knob by 0.04 to 0.07 second. But in six normal individuals, the pulmonary artery was ahead of the aortic knob by 0.06 second in one case. Thus the roentgenkymographic studies provide evidence for the frequent absence of mechanical ejection asynchronism in bundle branch block when records of ejection from both sides of the heart are studied. The same criticism can be made of Nichol's work.[11]



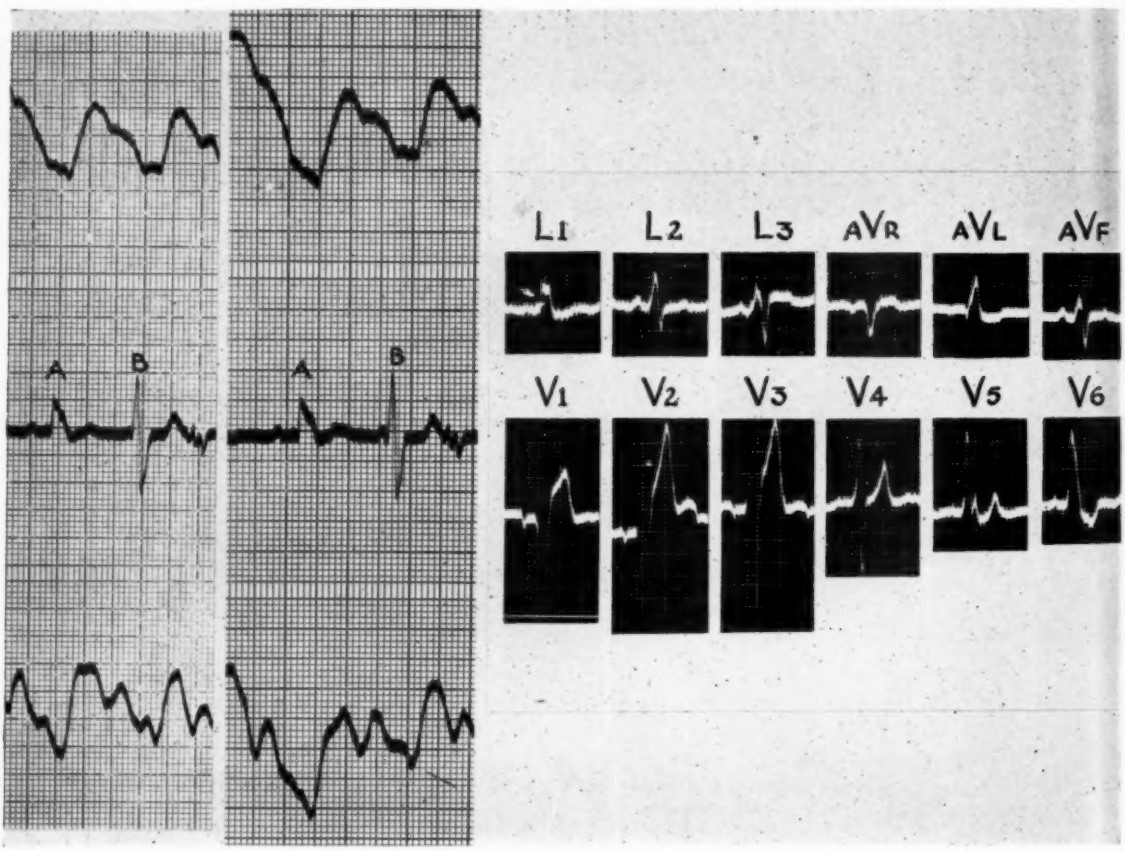
A. B.

Fig. 5.—Illustrating the results noted in W. C., a patient with complete right bundle branch block, QRS 0.16 second (Table II, Group B, Case 38) and with multifocal ventricular premature beats (Table VII, Case 10).

A, Lead I, and the electrokymograms of the ascending aorta and pulmonary artery, respectively, are noted from above down. Mechanical ejection asynchronism is partially present because in the beats related to the right bundle branch block (labelled X), the upstroke of the ascending aorta is 0.06 second ahead of the upstroke of the pulmonary artery, an abnormal relationship between the onset of ejection in the two great vessels. In these beats right-sided ejection is markedly delayed (QRS to ejection interval 0.20 second) while left-sided ejection is minimally delayed (QRS to ejection interval 0.14 second). The results noted with the ventricular premature beats are interesting. In the complex labelled A (a right ventricular premature beat), the upstrokes of the pulmonary artery and ascending aorta electrokymograms are identical in time. In complex B (a right ventricular premature beat), the ascending aorta upstroke is 0.02 second ahead of the pulmonary artery upstroke—a relation within normal limits. In complex C (a right ventricular premature beat), there is mechanical ejection asynchronism as the onset of pulmonary artery ejection is 0.05 second ahead of the onset of ascending aorta ejection. In complex D, however, (a left ventricular premature beat), the pulmonary artery is 0.01 second ahead of the ascending aorta—a relation within normal limits. It thus appears that correlation of mechanical ejection asynchronism with electrical asynchronism does not usually occur.

B, Shows the electrocardiogram of complete right bundle branch block with numerous ventricular premature beats also noted.

The work of Castex and associates[14] and that of Kossman and Goldberg[15] is subject to similar criticism. Both groups of investigators assumed that the presence of delayed ejection from one side of the heart permits the conclusion that mechanical ejection asynchronism is present without recording events from the opposite side of the heart. Furthermore, it should be noted that Castex and associates[14] found in seventy normal individuals that the onset of the QRS to carotid pressure wave interval was 0.12 second, while in the thirteen cases of left ventricular premature beats studied this same interval averaged 0.17 second. There is thus evidence of delayed ejection from the left side of the heart despite



A. B.

Fig. 6.—Showing the tracings in T. D., a patient with complete left bundle branch block with a QRS complex of 0.14 second (Table III, Case 5) and with left ventricular premature beats (Table VII, Case 5).

A, The electrokymogram of the ascending aorta, Lead I, and the electrokymogram of the pulmonary artery are noted from above down. In the left bundle branch complexes (labelled *A*), the pulmonary artery upstroke is 0.02 second ahead of the upstroke of the ascending aorta—a normal relation. In the two left ventricular premature beats (labelled *B*), the pulmonary artery upstroke is 0.01 to 0.02 second ahead of the ascending aorta upstroke—a normal relation. But note the delayed QRS ejection interval on both sides—0.22 for the left side and 0.20 for the right ventricle.

B, The electrocardiogram showing complete left bundle branch block.

the left ventricular origin of the premature contraction. It is very probable that mechanical ejection from the right ventricle was also delayed in these left ventricular premature beats, and further evidence for delayed ejection from both sides of the heart is, therefore, suggested in patients with abnormal ventricular depolarization.

The studies of Richards and Cournand and associates[16,17] must be discussed in more detail because these investigators have made records of mechanical events from both sides of the heart simultaneously, using an intracardiac catheter to record right ventricular and pulmonary artery pressures, and an indwelling needle in the brachial artery to record the peripheral arterial pulse wave. In two cases of left bundle branch block the onset of the QRS to onset of brachial artery pulse rise interval was markedly prolonged to 0.22 and 0.24 second (normal, 0.14 to 0.19 second; average, 0.16 second). In a third case of left bundle branch block this same interval to the femoral artery was 0.20 to 0.23 second. However, there was no value recorded for the interval from the onset of the QRS to the onset of the pulmonary artery pressure rise. Instead, comparison was made with the QRS to onset of right ventricular pressure rise interval which was normal (0.07 to 0.09 second) in these three cases. We feel that the validity of these deductions is open to question. In the left circuit the authors measured a QRS to ejection interval while in the right circuit the interval measured was from the onset of the QRS to the onset of right ventricular isometric contraction. If the latter phase were prolonged for the right ventricle (evidence for such prolongation has been found, Coblentz[17]), it is conceivable that a prolonged onset of QRS to onset of pulmonary artery ejection interval would have been found in these three cases of left bundle branch block. Essentially the measurements in these three cases suffer from the defect that ejection intervals were measured on one side of the circulation only. Studies were also made by these authors in five cases of right bundle branch block. In two of these patients the right bundle branch block was induced by quinidine and studies were therefore possible when the right bundle branch block was present and when it was absent. In both instances the onset of the QRS to onset of isometric contraction phase in the right ventricle interval was lengthened from 0.07 to 0.11 second with the development of the bundle branch block but the onset of QRS to onset of pulmonary ejection intervals were not reported. In one of these two instances the onset of the QRS to onset of the brachial artery pressure rise interval was 0.19 second before and after quinidine, but in the other insufficient data are available for complete study. In one of the three other cases of right bundle branch block the onset of the QRS to onset of isometric contraction in the right ventricle and onset of pulmonary artery pressure rise measured 0.13 and 0.15 second respectively, both markedly prolonged. In the same case the QRS to brachial artery interval measured 0.13 second. In this one case mechanical ejection asynchronism was completely demonstrated. In the remaining two cases again only QRS to right ventricular isometric contraction phase interval was measured and therefore ejection times were again measured only for the left side. In one of these last two cases the QRS to brachial artery interval was 0.24 second, showing delayed left ventricular ejection in a right bundle branch block.

We have reviewed in some detail the literature purporting to have demonstrated ventricular ejection asynchronism as a common occurrence in bundle branch block because we feel that unwarranted conclusions have been made from the data available. We feel that mechanical ejection asynchronism in bundle branch block and ventricular premature contractions has not been demonstrated in the literature, but that on the contrary our data indicate that such asynchronism occurs in only approximately one-third of such cases. Our data, and that of other investigators, do indicate that delayed ejection from both ventricles is a common occurrence in cases of bundle branch block and ventricular premature contractions.

The question of why electrical ventricular asynchronism is not accompanied by asynchronism in ventricular ejection is one that has not as yet been satisfactorily answered. Katz[12] has listed the following cogent arguments as to why one should not expect to find correlation between the electrical and mechanical ejection events of the cardiac cycle, especially with regard to asynchronism:

> "(1) A latent period exists between the onset of stimulation of the ventricles and the time when the electrical stresses so set up produce enough of a resulting potential to deflect the string of the electrocardiogram at ordinary sensitivity.
>
> "(2) A latent period exists between the onset of the QRS complex and the onset of mechanical systole as shown by intraventricular pressure curves in dogs. This latent period is not the same for both ventricles, there being a definite asynchronism in the dog of ± 0.01 to ± 0.03 second.
>
> "(3) A period of isometric contraction exists during which the left ventricle is getting up steam, as it were, before it begins to eject blood. This varies in duration in man.
>
> "(4) A time lag exists for transmitting the pulse from the aorta to the point of registration."

With regard to the third argument, it should be remembered that the isometric contraction phase varies considerably in duration in the two ventricles. This phase in the right ventricle measures 0.01 second in intact man (Coblentz and associates[17]). On the other hand, this same phase in the left ventricle measures from 0.02 to 0.06 second.[25,33-35] The marked differences in duration of the isometric contraction phase on the two sides of the heart may well be responsible for failure of correlation of electrical and mechanical ejection asynchronism, especially in cases of right bundle branch block where the longer isometric contraction phase of the left ventricle may partially at least negate the effects of delayed electrical activation of the right ventricle and make for more synchronous ejection from the two ventricles.

There are a number of papers in the literature which suggest that the mechanical and electrical events of the cardiac cycle can be separated. Mines[27] recorded the mechanical events of the frog's heart by a suspension method in which very fine silk threads were tied to the tips of the auricle and ventricle. An electrocardiogram was recorded simultaneously. Mines noted that perfusion of the

frog's heart with a calcium-free solution resulted in almost complete cessation of the mechanical beat, while the simultaneously recorded electrocardiogram remained unchanged. Bertha[28] and Bertha and Schutz[29] have also noted that mechanical contraction of the heart can be stopped while the electrocardiogram continues unchanged. Garb,[30] in a series of experiments on isolated cat papillary muscle, has noted that a normal electrocardiogram of the papillary muscle can be obtained in the absence of any measurable contractile force by perfusion of the muscle with a fluid containing low levels of calcium. These observations suggest that failure to find correlation of mechanical ejection and electrical asynchronism should not be regarded with surprise.

A further possible explanation for the absence of such correlation may again be related to the ventricular isometric contraction phase. This interval is defined as the period between the onset of the systolic pressure rise in the ventricle and the systolic pressure rise in the corresponding great vessel, or as the period between the onset of mechanical ventricular systole and the opening of the corresponding semilunar valve. Since the auriculoventricular valve is closed at the onset of the ventricular pressure rise, the ventricle is a closed chamber during this period. The ultimate duration of this phase must in large part depend upon the diastolic pressure differentials between the ventricle and the corresponding great vessel. For example, normally the diastolic pressure in the ascending aorta is about 70 mm. Hg, while that in the left ventricle is very much less, and is probably close to 0. On the right side, however, the diastolic pressure in the pulmonary artery is about 8 mm. Hg while that in the right ventricle is 1 to 2 mm. Hg. Obviously, the left ventricle must raise a much greater head of pressure to open the aortic valve than must the right ventricle to open the pulmonic valve. It is to be expected that the duration of the isometric contraction phase will vary if the diastolic pressure in the great vessel varies. Coblentz and associates,[17] as noted above, have found the normal isometric phase of the right ventricle to be 0.01 to 0.02 second, average 0.013 second in fifteen cases, employing intracardiac catheterization to determine the onset of the systolic pressure rise in the right ventricle and pulmonary artery simultaneously. However, in children with congenital heart disease, Coblentz and associates[17] have noted a prolongation of the isometric contraction phase of the right ventricle, despite the fact that the other phases of the cardiac cycle were shorter than those of normal adults. The increase in the duration of isometric contraction was ascribed to hypertension in the lesser circuit. One case was cited where the duration of isometric contraction was 0.030 second before ligation of a patent ductus arteriosus (with pulmonary hypertension) but was reduced to 0.01 second after operation when the pulmonary hypertension disappeared. In congestive heart failure with pulmonary hypertension in adults, Coblentz and associates[17] also noted prolongation of the right ventricular isometric contraction phase. Since prolongation of the isometric contraction phase must result in prolongation of the QRS to ejection interval, it is quite conceivable that changes in ascending aorta or pulmonary artery diastolic pressures could cause the failure of correlation of electrical and mechanical ejection asynchronism. For example, in a patient with left bundle branch block with pulmonary hypertension due to congestive heart failure, the lesser circulation hypertension could result in an increased duration of the right

ventricular isometric contraction phase and a delayed right ventricular ejection, and thus result in the delayed left ventricular ejection (with left bundle branch block) being delayed no more, perhaps, than right ventricular ejection. Under these circumstances the QRS to ejection interval would be delayed for both sides of the heart, but ejection asynchronism would be absent if this delay was in the same range for both sides of the heart. On the other hand, in right bundle branch block the presence of systemic arterial hypertension could also result in a delayed left ventricular ejection and again obscure ejection asynchronism from the ventricles. If this hypothesis were true, it might follow as a corollary that while ejection asynchronism does not occur, mechanical asynchronism in onset of the isometric contraction phase of the two ventricles does occur. Unfortunately we could not uniformly record the onset of isometric contraction of the two ventricles simultaneously to test this theory. Furthermore, since we have no data on the pressure in the lesser circuit in our cases (though many did have essential hypertension), the above thesis must remain only a hypothesis. The evidence for delayed ejection from both sides of the heart in many cases of bundle branch block must be regarded as established on the basis of our results and the results of Coblentz[17] and Richards.[16] In this connection we must state, however, that we have studied twelve cases of so-called congenital right bundle branch block in young men with no clinical or laboratory evidence of cardiovascular disease. The systemic blood pressure was normal in all twelve. Since it can safely be assumed that pulmonary hypertension was absent in this group, our failure to find correlation between electrical and ejection asynchronism in more than four of the twelve cases suggests that the above-mentioned hypothesis does not apply, at least to this group.

One last fact should be brought out. At post-mortem examination, lesions in both bundle branches are more commonly found[1,2] than lesions in one bundle branch, despite the demonstration of bundle branch block on one side only by the electrocardiogram. With this in mind, delayed ejection from both ventricles should be the rule rather than delayed ejection from one side and consequent asynchronous ejection.

SUMMARY

In a study of eighty-three cases of bundle branch block, two cases of complete heart block with idioventricular rhythm, and twenty-one ventricular premature beats in fourteen patients, the mechanical ejection events of the greater and lesser circulation were recorded simultaneously by electrokymograms of the ascending aorta and pulmonary artery. We failed to find mechanical ejection asynchronism accompanying the electrical asynchronism in about 70 per cent of the cases. We did, however, find evidence of delayed ejection from both ventricles in the majority of cases. Several possible explanations for our findings are discussed.

We would like to express our gratitude to Dr. Arthur C. DeGraff, Senior Consultant to the Medical Service, Bronx Veterans Hospital, for the aid and encouragement which made the work possible.

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SUBENDOCARDIAL MYOCARDIAL INFARCTION WITH SPECIAL REFERENCE TO THE ELECTROCARDIOGRAPHIC CHANGES

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THE early descriptions of the electrocardiographic distinction between anterior and posterior myocardial infarction are well known and confirmed.[1-3] The introduction of precordial leads[4,5] has aided the more precise diagnosis of anterior myocardial infarction. Likewise, the use of the esophageal leads[6,7] and of the unipolar limb leads[8-11] aids the diagnosis of posterior myocardial infarction. It has been suggested that lateral myocardial infarction, although comparatively uncommon, is a third distinct type and seems to have its own electrocardiographic pattern.[12,13]

There is still another group of cases of myocardial infarction in which only the subendocardial layer is involved and the subepicardial layer appears normal. Of forty-nine patients with myocardial infarction, in 1,000 consecutive postmortem examinations, there were three with diffuse infarction beneath the endocardium.[14] From 1942 to 1945 five similar patients showed unusual electrocardiographic changes before death.[15-18] At autopsy the subendocardial layer of the left ventricle was the only site of infarction, and in four patients the interventricular septum was also involved. The case reported by Bayley[17] showed persistent, marked depression of the RS-T segment in Leads I, II, and CF_4 and no significant change in Lead III. These changes were interpreted as indicating greater injury at the endocardial than at the epicardial surface. Pardee and Goldenberg[19] reported a series of twelve unusual instances of anterior myocardial infarction, including several without subepicardial necrosis, in which the tracings resembled those seen after exercise, anoxemia tests, and during angina. Case 4 showed marked RS-T depression in Leads I, II, and CF_4; pathologically, the process was entirely subendocardial. Myers and his associates,[20,21] however, were unable to correlate the electrocardiographic and pathological findings in a large number of cases of subendocardial infarction. Whitten[22] described three distinct pathological types of myocardial infarction, one of which consisted of lesions confined to the endocardial portion of the ventricular wall, due to occlusion of the larger subendocardial branches of the coronary arteries in the musculature.

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Wolferth and his co-workers (1945)[23] in an excellent experimental study pointed out that extensive trauma to the endocardial side of the myocardium in dogs produces a negative displacement of RS-T segment with the recording electrode at the ventricular epicardial surface. Hellerstein and Katz (1948)[24] demonstrated that localized injury of the subendocardium (exclusive of the interventricular septum) resulted in: 1) RS-T depression and minimal change in the amplitude of the R and S waves in leads over the epicardial surface superjacent to the injury, and 2) RS-T elevation in leads from the heart cavities. Hence the subendocardial, subepicardial, intramural, or transmural location of the injury of the ventricular wall is important.

CASE MATERIAL AND METHODS

From August, 1948, to January, 1950, inclusive, seven patients with subendocardial infarction of the left ventricle were observed clinically, and the diagnosis was confirmed at autopsy. Five of these seven patients were correctly diagnosed ante mortem on the basis of the electrocardiographic changes, whereas bundle branch block obscured the findings in the other two. Sixteen patients with electrocardiographic changes highly suggestive of subendocardial myocardial infarction of the left ventricle have also been observed. One of these had two attacks of subendocardial myocardial infarction within a year.

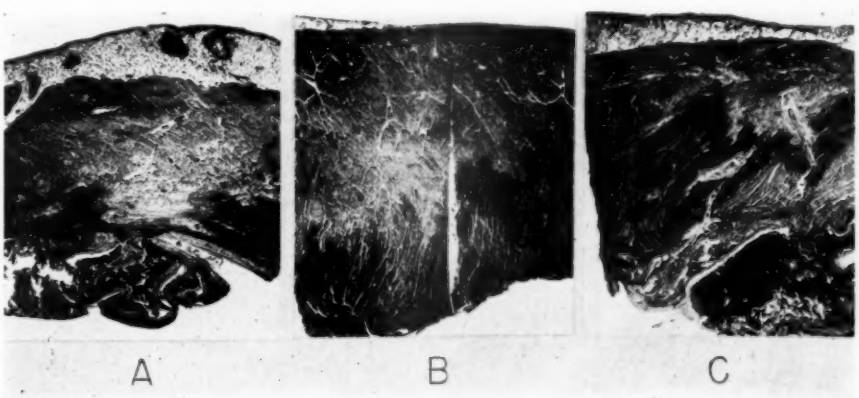


Fig. 1.—Photomicrographs of the myocardium of three patients (× 7.5). The epicardium is on the top and the endocardium at the bottom. The infarctions are seen in the subendocardial layers. *A*, Case 1; *B*, Case 3; and *C*, Case 5.

One or more electrocardiograms consisting of three standard limb leads, three augmented unipolar limb leads, and three or more precordial leads (usually V_2, V_4, and V_5) were obtained in every case except two in which only three standard limb leads and three precordial leads (CF_2, CF_4, and CF_5) were taken. The anatomic location and age of the infarct are described as accurately as possible and the illustrations of the microscopic sections of three proved cases are reproduced (Fig. 1).

TABLE I. THE OUTSTANDING FEATURES AND ELECTROCARDIOGRAPHIC CHANGES IN TWENTY-THREE PATIENTS WITH SUBENDOCARDIAL MYOCARDIAL INFARCTION

CASE NO.	AGE AND SEX	HISTORY OF			SYMPTOMS AND SIGNS ON ADMISSION				IMPORTANT ELECTROCARDIOGRAPHIC CHANGES	COURSE
		HYPERTENSION	ANGINA PECTORIS	PREVIOUS MYOCARDIAL INFARCTION	SUBSTERNAL PAIN	REDUCTION OF BLOOD PRESSURE	ENLARGEMENT OF HEART	CONGESTIVE HEART FAILURE		
SEVEN PROVED CASES										
1	54 M	–	+	–	+	+	+	+	Fig. 2	Died
2	58 F	+	–	–	+	+	+	+	Fig. 3	Died
3	69 F	+	+	+	+	+	+	+	1. RS-T change 2. Left BBB	Died
4	64 F	+	–	–	+	–	–	+	Fig. 4, A	Died
5	54 M	–	+	+	+	–	+	+	1. RS-T change 2. Right BBB	Died
6	72 M	+	?	–	?	+	+	+	1. RS-T change 2. Decrease in R	Died
7	82 F	+	+	–	+	+	+	+	1. RS-T change 2. Decrease in R 3. Small Q	Died
SIXTEEN PROBABLE CASES										
8	59 F	+	–	–	+	–	+	+	1. RS-T change 2. Decrease in R 3. Notching of R	Well
9	67 M	?	+	+	+	+	–	–	1. RS-T change 2. Small Q	Well
10	68 F	+	+	+	+	+	+	+	1. Transient left BBB 2. Later RS-T change Decrease in R	Well

11	52 M	+	−	−	−	−	+	+	RS-T change	Well
12	86 F	+	+	?	+	+	+	+	1. RS-T change 2. PR prolongation 3. Increase in S	Well
13	57 M	+	+	−	+	−	+	+	RS-T depression and small Q in Leads II, III, and aV_F	Well
14	52 F	+	+	?	+	+	+	+	RS-T change	Well
15	67 F	+	−	−	−	+	+	+	1. RS-T change 2. Small Q	Well
16	48 M	+	+	−	+	+	−	−	1. RS-T change 2. Decrease in R	Well
17	65 M	−	+	?	+	+	−	+	RS-T change	Died No autopsy
18*	60 M	+	+	?	+	−	[illegible]	+	1. RS-T Change 2. Small Q	Well
19*	58 F	+	+	−	+	−	+	−	1. RS-T change 2. Decrease in R	Well
20	75 M	−	+	−	+	+	−	+	1. RS-T change 2. Decrease in R 3. Transient left BBB 4. PR prolongation	Well
21	67 F	+	+	−	+	+	−	+	1. RS-T change 2. Transient left BBB	Well
22	71 M	+	+	−	−	+	+	+	1. RS-T change 2. Decrease in R	Well
23	70 F	+	−	−	−	−	+	+	1. RS-T change 2. Transient left BBB	Well

+ present, − absent, ? doubtful.

RS-T change—depression in Leads I, II, aV_L, and V_{3-6} with elevation in Lead aV_R.

Decrease in R
Notching of R
Small Q
Increase in S } indicating changes in the QRS complex, usually in the left percordial leads, and less often in Leads I and aV_L.

BBB—bundle branch block.

*We wish to thank Dr. F. Anderson, The Genesee Hospital, Rochester, N. Y., for the clinical data of Cases 18 and 19.

RESULTS

The pertinent clinical features and electrocardiographic changes of twenty-three cases of subendocardial myocardial infarction are presented in Tables I and II.* History of hypertension, angina pectoris, and previous myocardial infarction was recorded in 78, 70, and 17 per cent of the patients, respectively. Severe substernal pain was present in 78 per cent of patients. In more than half of the patients there was reduction of blood pressure. Enlargement of heart was found in 75 per cent and signs of congestive heart failure were observed in more than 80 per cent of the patients.

The essential pathological findings post mortem are tabulated in Table III.

TABLE II. THE OUTSTANDING CLINICAL FEATURES OF TWENTY-THREE PATIENTS WITH SUBENDOCARDIAL MYOCARDIAL INFARCTION

CLINICAL FEATURES	PROVED CASES (7)	PROBABLE CASES (16)	TOTAL CASES (23)	PER CENT
History of:				
Hypertension	5	13	18	78
Angina pectoris	4	12	16	70
Previous myocardial infarction	2	2	4	17
Symptoms and Signs on Admission:				
Severe substernal pain	6	12	18	78
Reduction of blood pressure	5	10	15	65
Enlargement of heart	6	11	17	74
Congestive heart failure	7	13	20	87
Characteristic Electrocardiographic Changes	5*	16	21	91

*The electrocardiographic changes of the other two patients were obscured by the presence of bundle branch block.

DISCUSSION

General Considerations.—The studies by Myers and his associates,[20,21] together with the present report suggest that the incidence of subendocardial myocardial infarction is not small. The outstanding clinical features of most of the cases reported in the present series were evidence of previous heart disease, history of hypertension and angina pectoris, presence of severe substernal pain prior to admission, and reduction of blood pressure, signs of congestive heart failure, and characteristic electrocardiographic changes on admission (Tables I and II). But clinically, without the aid of electrocardiograms, one cannot possibly differentiate this type of infarction from the ordinary type of anterior or posterior myocardial infarction with transmural or predominantly subepicardial lesion.

Subendocardial myocardial infarction may or may not be associated with coronary occlusion. Three of the five isolated cases reported in the literature[16-19] had no evidence of occlusion of the coronary arteries. In the present series of seven proved cases, there was coronary occlusion in four.

*The details of the post-mortem findings are incorporated in the appendix.

From the available data of the post-mortem examination and the changes in the electrocardiograms of the patients with subendocardial myocardial infarction, the most common sites of the infarcts are in the inner aspect of the anterolateral wall and the interventricular septum of the left ventricle. The posterior or diaphragmatic wall of the same ventricle is much less frequently involved. The prognosis for patients with this lesion should be guarded since a 30 per cent mortality was observed.

Electrocardiographic Changes in Subendocardial Myocardial Infarction (Figs. 2, 3, 4, and 5).—Since the endocardial surface is nourished by a comparatively rich arterial plexus and in case of impaired coronary flow it may be irrigated by blood which flows through the Thebesian veins, it differs from the epicardial surface.[25] Consequently, when "a large zone of local ventricular ischemia develops and reaches the transmural proportions, the intensity tends to be greater in the subjacent epicardial, than in the subjacent endocardial, muscle."[25] This

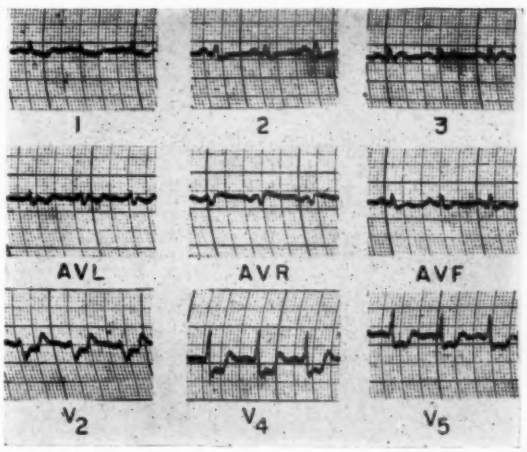


Fig. 2.—Electrocardiogram of Case 1, taken on Nov. 28, 1948. Note low voltage and RS-T depression in Leads I, II, V_2, V_4, and V_5, and RS-T elevation in Lead aV_R.

explains why in an ordinary case of myocardial infarction the electrocardiogram will show more intense injury current displayed by the subepicardial layer than by the subendocardial layer.[26] Therefore, in anterolateral myocardial infarction RS-T elevation is seen in Leads I, aV_L and V_{3-6} whereas in posterior myocardial infarction RS-T elevation occurs in Leads II, III, and aV_F. The elevation of RS-T segment in one group of leads is usually associated with depression of RS-T segment in the other group of leads.

On the other hand, the presence of infarction in the subendocardial layer alone will show quite different electrocardiographic changes. In the present series, the most constant and characteristic findings in the electrocardiograms in five out of seven proved cases, and in all probable cases, was marked depression of RS-T segment in Leads I, II, aV_L, V_4, and V_5. The magnitude of depression sometimes was as much as 5 or 6 mm. below the isoelectric line. There was usually no significant change of the RS-T segment in Leads III or aV_F, except

TABLE III. PATHOLOGICAL FINDINGS POST MORTEM IN SEVEN PATIENTS WITH SUBENDOCARDIAL MYOCARDIAL INFARCTION

CASE	HEART WEIGHT (GM.)	DILATATION OF HEART	THICKNESS OF VENTRICULAR WALL (CM.)		MYOCARDIAL LESIONS GROSS / MICROSCOPIC		ESTIMATED DURATION OF INFARCTION (DAYS)	SEPTAL LESIONS	CORONARY VASCULAR LESIONS	VALVULAR LESIONS
			RIGHT	LEFT	SUBEPICARDIAL	SUB-ENDOCARDIAL				
1	380	All chambers	0.5	0.9	None Capillary engorgement and hemorrhage	Infarction, mural thrombus Infarction, recent and old (Fig. 1, *A*)	1 to 4 and 20 to 30	Left ventricular surface	Occlusion of both coronary arteries	None
2	650	All chambers	0.5	2.0	None Scattered fibrous tissue	Mural thrombus Extensive infarction	30	Left ventricular surface	No occlusion, arteriosclerotic plaques in both coronary arteries	Aortic stenosis
3	425	Left auricle	0.5	1.9	None Scattered fibrous tissue	Infarction Infarction, recent and old (Fig. 1, *B*)	1 to 4 and 30	None	Occlusion of right coronary artery	Thickening of mitral valves

4	330	Left auricle	0.3	1.2	None A few small areas of early necrosis	Infarction Extensive infarction	1 to 3	Left ventricular surface	No occlusion, arteriosclerotic plaque in left coronary artery	None
5	580	Both ventricles	0.6	1.5	Small epicardial hemorrhage Early necrosis in a small area	Infarction Extensive infarction (Fig. 1, *C*)	4 to 7	Left ventricular surface	Occlusion of left coronary artery	None
6	420	Left ventricle	0.5	1.5	Slight epicardial adhesion Scattered fibrous tissue	Infarction Infarction, recent and old	4 to 8 (recent)	Left ventricular surface	Occlusion of both coronary arteries	Thickening of aortic and mitral valves
7	400	Left ventricle	0.4	1.8	None Scattered fibrous tissue	Infarction Extensive infarction	8 to 14	Left ventricular surface	No occlusion, narrowing of orifices of both coronary arteries	Thickening of mitral and tricuspid valves

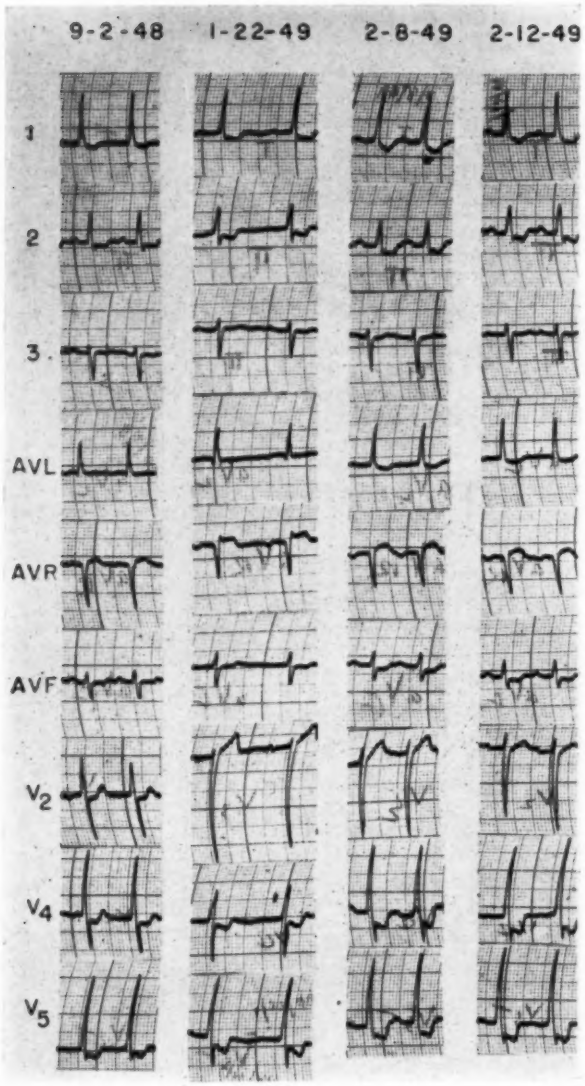
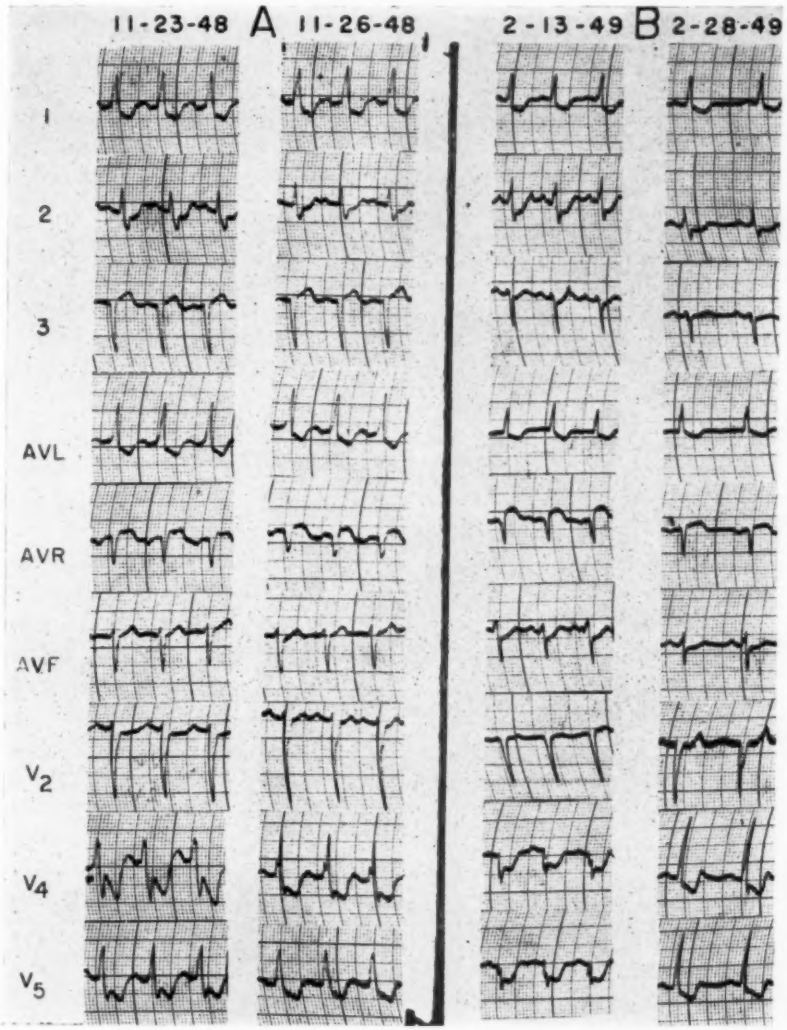


Fig. 3.—Case 2. Tracings taken on Sept. 2, 1948, showed evidence of left ventricular hypertrophy. In the subsequent tracings there was marked RS-T depression in Leads I, II, V_4, and V_5 and RS-T elevation in Lead aV_R.

that in one tracing RS-T depression occurred in Leads II, III, and aV_F. This patient was suspected of having had subendocardial infarction of the posterior layer of the left ventricle. Definite RS-T elevation in Lead aV_R was the most characteristic finding. Since this lead reflects the intracavity potential variations[27,28] it is conceivable that a lesion in the subendocardial layer of the myocardium would produce RS-T elevation in Lead aV_R. These findings are in full agreement with those which have been observed in recent animal experiments with subendocardial lesions of the myocardium.[21,24] During recovery the de-



A. B.

Fig. 4.—*A*, Case 4. There was marked RS-T depression in Leads I, II, aV_L, and V_4 and V_5 and abnormal RS-T elevation in Lead aV_R. Note the decrease in amplitude and notching of R wave in Leads V_4 and V_5.

B, Case 6. Same findings as in Case 4 except for more marked decrease in amplitude and absence of notching of R wave in Leads V_4 and V_5.

pression of RS-T segment usually became less marked but in a few patients it persisted for more than two weeks.

Changes in the QRS complex were observed in more than one-half of the tracings. These consisted of, in decreasing order of frequency, appearance of Q wave, decrease in the amplitude of R wave, notching of R wave and increase in the amplitude of S wave in one or more of the precordial leads. In a few cases a distinct but small Q wave developed in Leads I, aV_L, V_4, and V_5. This

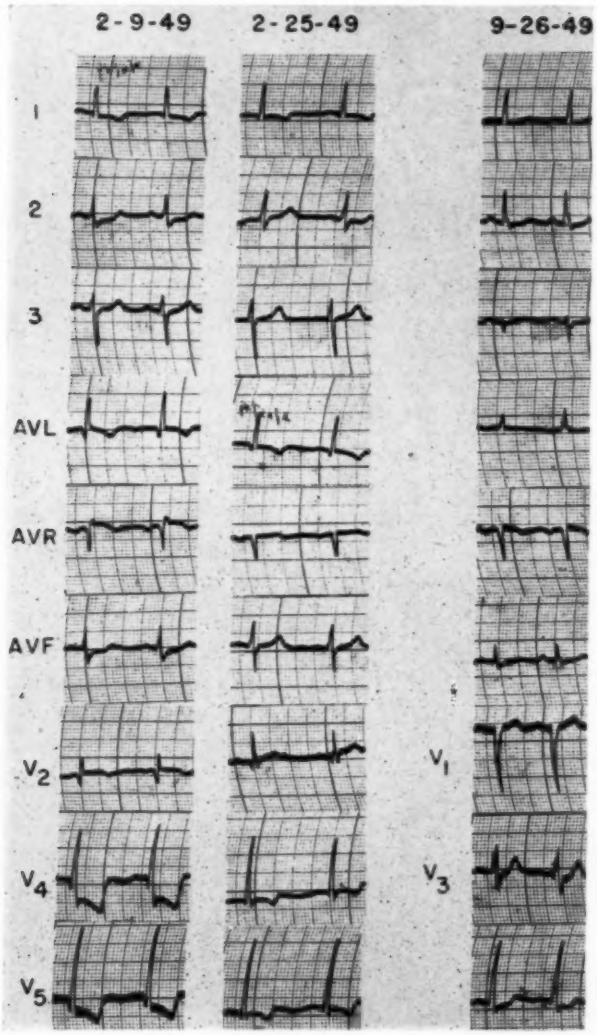


Fig. 5.—Case 7. Tracings taken on Feb. 9, 1949, showed presence of a small Q wave in Leads I, aV_L, V_2, V_4, and V_5, marked RS-T depression in Leads II, V_4, and V_5, and abnormal RS-T elevation in Lead aV_R. On Feb. 25, 1949, the changes were less prominent and on Sept. 26, 1949, the electrocardiogram was almost normal except for slight RS-T depression in Leads II, aV_F, V_3, and V_5.

Q wave either persisted for a long time or disappeared as the patient was convalescent. In other cases decrease in amplitude of R wave together with increase in amplitude of S wave was quite definite. Recently, it has been emphasized by Myers and his associates[20,21] that if more precordial leads are used, one should be able to obtain a QR pattern or a notched QS deflection in most of the cases. Notching of the QRS complex has been mentioned by Bayley[17] as possible evidence of morphologic death of some regions of the ventricular wall.

Bundle branch block occurred in seven patients, three of whom died. In the remaining four patients the bundle branch block was transient in nature.

The presence of bundle branch block may completely obscure the typical changes of subendocardial myocardial infarction (Case 3). Hellerstein and Katz[24] in animal experiments have shown that injury of the subendocardium, on rare occasions, produces QRS prolongation in region of injury.

Transient complete auriculoventricular block was present in one case and prolonged P-R interval was observed in three cases. Occasional auricular and ventricular premature beats were seen in four cases. In no case was auricular fibrillation or flutter a complication of the infarction.

The T wave was usually inverted in Leads I, II, aV_L, V_4, and V_5 and often upright in Lead aV_R. The corrected Q-T interval was prolonged in most of the cases.

Differential Diagnosis of Conditions Which Produce Marked RS-T Depression.—

1. *Lateral Infarction:* In 1938, Wood, Wolferth, and Bellet[12] described the characteristic pattern of the electrocardiogram in lateral infarction which consisted of (a) depression of RS-T segment in Leads I, II, and CF_4 or CR_4 and (b) an absence of sign of posterior infarction in Lead III. The QRS complex seemed to be significantly unaffected. This group of patients had a very high incidence of auricular fibrillation. The electrocardiographic pattern could be mimicked in certain cases by digitalis action and changes in the electrocardiogram in acute lesions might subside rapidly. Three patients came to autopsy with evidence of lateral infarction but no mention was made about the layers of the myocardium involved. In one of their subsequent communications,[23] the RS-T depression was explained on the basis that the electrodes were placed outside the zone of maximal injury and secondary RS-T changes were produced. Later on, Thomson and Feil[13] analyzed the electrocardiograms obtained on nineteen patients with post-morten evidence of lateral infarction and found the typical pattern described by Wood, Wolferth, and Bellet in only four. In one of the typical cases reported by Thomson and Feil the marked RS-T depression in the precordial leads aroused the suspicion that subendocardial infarction might be present and it was subsequently shown that the predominant lesion was actually in the subendocardial muscle.[17]

Beside the typical pattern described above, these investigators have also included the atypical pattern which consisted mainly of RS-T elevation in Leads I and CF_4 or CR_4 or in Leads II and III. Shaffer[29] in a similar report based on the study of five patients with lateral infarction with autopsy findings revealed that no consistent or characteristic pattern could be found at all. Myers and his associates[21] classified twenty-seven cases of lateral infarction into three groups according to the distribution of the lesions: (a) high, (b) low, and (c) mid-lateral infarction. It is interesting to note that those cases with a pattern resembling that described by Wood, Wolferth, and Bellet had a lateral infarction involving the subendocardial layer only.

It is our belief that whenever only the subendocardial layer of the anterolateral or lateral wall of the left ventricle is infarcted one would expect to find RS-T depression in Leads I, II, aV_L, V_4, V_5, and V_6 and RS-T elevation in Lead aV_R. On the contrary, when the infarction of the lateral wall is transmural

or involves predominantly the subepicardial layer there is usually RS-T elevation in Leads I, aV_L, and precordial leads superjacent to the lesion. Furthermore, the RS-T segment in Lead aV_R is either depressed or isoelectric.

2. *Posterior Infarction:* In acute posterior myocardial infarction, associated with the characteristic RS-T elevation in Leads II, III, and aV_F there is not infrequently marked depression of the RS-T segment in one or more of the precordial leads. In a few cases of acute posterior infarction observed by us the RS-T segment was markedly depressed in V_4 and V_5, and with low voltage in the limb leads the RS-T segment in Leads II, III, and aV_F was only slightly elevated. We have had some difficulty in differentiating this condition from subendocardial myocardial infarction. But in serial tracings the evidence of posterior infarction became more definite and the RS-T change in the precordial leads promptly disappeared. The changes of the RS-T segment in Lead aV_R sometimes are helpful in differentiating these two conditions. In a series of twenty cases of acute posterior infarction[30] the RS-T segment in aV_R was depressed in two, isoelectric in eleven, slightly elevated in six, and moderately elevated in only one. On the contrary, in cases of subendocardial myocardial infarction RS-T elevation in this lead is the rule.

3. *Coronary Insufficiency and Angina Pectoris:* There are three main causes of coronary insufficiency:[31] (a) increased cardiac work, such as exertion and tachycardia; (b) diminished coronary flow, such as shock, hemorrhage and operation; and (c) impaired oxygenation of the blood, such as anesthesia and asphyxia. The electrocardiographic changes in these conditions are characterized by RS-T depression, which is usually reversible and of short duration. All these are evidently due to the inability of the coronary circulation to meet the demand of the myocardium for oxygen in patients with diseased coronary vessels. Presumably the subendocardial layer of the myocardium suffers the most during coronary insufficiency.

Out of forty-eight cases of acute coronary insufficiency with myocardial infarction fifteen showed a definite depression of the RS-T segment in limb leads, and less frequently in the precordial lead.[32] Usually the infarcted areas were localized to the subendocardium and the papillary muscles of the left ventricle. It is probable that coronary insufficiency of long duration may eventually lead to subendocardial myocardial infarction. In cases of coronary insufficiency without infarction, however, the duration of RS-T depression is usually short and the QRS complex as a rule shows no significant changes.

The characteristic changes in the electrocardiogram in an attack of angina pectoris consist mainly of transient RS-T depression in Lead I and one or more of the precordial leads.[33,34] Electrocardiographic pattern resembling that of an acute myocardial infarction has been observed,[35,36] but this is distinctly rare.

4. *Digitalis Effect or Intoxication:* Digitalis produces depression of RS-T segment in most of the limb leads, and left precordial leads (except in Lead aV_R in which the RS-T segment is usually elevated). Marked RS-T depression can occur with digitalis intoxication, but the mechanisms of the electrocardiographic changes are not clearly understood. Experimental studies in animals have shown that digitalis intoxication may produce marked hemorrhage and

damage in the subendocardial layer of the myocardium.[37,38] It also has been suggested that the anoxemia may be one of the many factors involved in the production of myocardial lesion by digitalis.[39] In our experience the RS-T depression in the precordial leads rarely exceeds 4 mm. below the isoelectric line, and the corrected Q-T interval is always *shortened* in relation to value prior to digitalis therapy.

SUMMARY AND CONCLUSIONS

(1) Twenty-three cases of subendocardial myocardial infarction, in which only the endocardial layer is involved and the epicardial layer appears essentially normal, are described. The fatality rate was around 30 per cent.

(2) Five of the seven proved cases were diagnosed ante mortem on the basis of the characteristic electrocardiographic changes. The clinical, electrocardiographic, and pathological data of these cases are reported in detail.

(3) The most characteristic changes in the electrocardiograms consist of (A) marked depression of RS-T segment in Leads I, II, aV_L, and V_{3-6}, and (B) definite elevation of RS-T segment in aV_R. The RS-T segment changes usually *persist* for several days.

(4) The relationship of these findings to recent electrocardiographic theory, and the differential diagnoses are discussed.

APPENDIX

CASE 1.—

Gross Pathology: The heart weighed 380 grams. The epicardial surfaces appeared normal. All chambers were dilated. The valves were essentially normal. The left ventricle was soft and flabby, measuring 9 mm. in thickness, the right ventricle 5 mm. On section the entire left ventricle was gray-yellow in color with several irregular, softened, sharply demarcated brown, gelatinous areas from 2 to 6 mm. in diameter. The interventricular septum was generally yellow-gray in color with some reddish-brown discoloration in the anterior-superior portion. About 1.5 cm. from the ostium of the left coronary artery there was a thickened arteriosclerotic plaque with a superimposed thrombus completely occluding the artery. This thrombus extended 1.5 cm. to the bifurcation of the left coronary artery, but the branches of the latter were patent except at one point halfway down in the anterior descending branch where there was a yellow-white mass occluding its lumen. About 3 cm. from the ostium of the right coronary artery was a thickened area with a mass of clotted brown material filling the lumen.

Microscopically, the epicardium was normal. The capillaries and venules of the subepicardial fat were dilated and engorged. In a few areas there were small hemorrhages. The superficial layers of the left ventricle were normal (Fig. 1,*A*). The endocardial half showed necrosis of muscle fibers with marked polymorphonuclear and macrophage infiltration. In another section, also from the left ventricle, the majority of the infarcted muscle was again in the endocardial half, but there were a few small areas of absent fibers and macrophage infiltration close to the epicardial fat. There were also areas of older infarction as indicated by fibrosis and vascularization in areas of muscle replacement.

The estimated durations of the two recent infarcts were approximately 1 to 4 days and 20 to 30 days, respectively. There was a mural thrombus without organization among the papillary muscles. The blood vessels of the myocardium of the left ventricle and interventricular septum were engorged and erythrocytes were found in an occasional dilated lymphatic.

Anatomic Diagnoses: Coronary arteriosclerosis, recent thrombosis of left coronary artery, myocardial infarction of the left ventricle (subendocardial), cardiac dilatation, and small mural thrombus.

CASE 2.—

Gross Pathology: There were a few fibrinous and fine fibrous adhesions of the pericardium. The heart weighed 650 grams. The epicardium was smooth and glistening. All chambers were dilated. The aortic cusps were thick, rigid, and calcified, the opening barely admitting a probe. The left ventricle measured 2 cm. and the right 0.5 cm. in thickness. The myocardium was generally of a healthy brown color and firm in consistency. There was a mural thrombus of 1 cm. in size at the apex of the left ventricle, adjacent to the interventricular septum beneath which the myocardium was thinned to 4 mm. The myocardium in that region seemed pale as did the adjacent papillary muscle. Section through the posterior surface of the left ventricle showed scattered small areas of fibrosis of the myocardium. The coronary ostia were patent but somewhat narrowed by arteriosclerotic change in the aortic cusps. There were arteriosclerotic plaques in the proximal portion of both coronary arteries but the more distal portions showed rather smooth intima.

Microscopically, in the epicardium from left ventricle there were multiple small areas of replacement of muscle by fibrous tissue of varying density. These changes were most marked in the myocardium of the apex. An organizing mural thrombus was seen on the endocardium, beneath which the myocardium showed replacement of young, well-vascularized fibrous tissue. The estimated duration of the infarct was approximately one month.

Anatomic Diagnosis: Coronary arteriosclerosis; old myocardial infarction of left ventricle with recent subendocardial involvement; mural thrombus, left ventricle, organizing; marked calcific aortic stenosis; and cardiac hypertrophy.

CASE 3.—

Gross Pathology.—The heart weighed 425 grams. The epicardium contained a few, small, milky patches over the anterior left ventricle. The left auricle was dilated. The mitral valve was thickened and calcified with fusion of chordae tendinae. The left ventricle measured 1.9 cm., and the right 0.5 cm. in thickness. Cut section through the anterior left ventricle showed its outer layers to be a healthy beefy-red color with minimal number of small areas of fibrous tissue. The inner layer just beneath the anterior papillary muscle showed a sharply defined area of mottled yellow-red color and firm consistency. The right coronary ostium was completely occluded and the right coronary artery could not be dissected due to marked thickening of its wall and narrowing of its lumen. The wall of the left coronary artery was thickened and calcified with marked narrowing of the lumen in both its branches. No thrombi were found.

Microscopically, there were dense fibrous and hyaline connective tissue plaques in the epicardium. There were scattered areas of fibrosis in the myocardium. A section (Fig. 1, *B*) from the left ventricle including an anterior papillary muscle showed a large sharply defined area of subendocardial infarction, with cloudy swelling, hydropic degeneration, early necrosis of the muscle fibers with loss of nuclear detail, and hemorrhage between the fibers. No polymorphonuclear infiltration was present. The estimated duration of the recent infarct was around 1 to 3 days and of the others approximately one month.

Anatomic Diagnoses: Coronary arteriosclerosis with old occlusion of right coronary artery; recent myocardial infarction of left ventricle (subendocardial); old myocardial scars; chronic rheumatic mitral endocarditis with mitral stenosis; and cardiac hypertrophy and dilatation of left auricle.

CASE 4.—

Gross Pathology: The heart weighed 330 grams. There were numerous small petechiae in the epicardial surface which had a dull granular appearance over the lateral and posterior surface of the left ventricle. The left auricle was dilated and mural thrombi were present in both auricles. The endocardial surface in the posterolateral aspects of the left ventricle was of a mottled yellow-tan color. On cut section the posterior and lateral portions of the left ventricle were mottled yellow-red and tan in color, principally in the endocardial half of the myocardium. There was some yellow streaking in the interventricular septum. The right ventricle was normal in appearance. The coronary vessels were of normal caliber except for the circumflex branch of the left coronary artery, the lumen of which was markedly narrowed by a few small atheromatous plaques. There was no thrombus found.

Microscopically, the epicardium appeared normal. There were patchy areas showing the early changes of infarction, largely in the endocardial half of the left ventricle but in a few small areas in the subepicardial half. These consisted of even, pink, granular anuclear fibers, with a few areas showing extravasated erythrocytes and a rare area of polymorphonuclear-cell infiltration. The intraventricular septum showed evidence of hydropic degeneration and scattered areas of early infarction. The right ventricle appeared normal. The estimated duration of the recent infarct was 1 to 3 days.

Anatomic Diagnoses: Coronary arteriosclerosis with narrowing of the circumflex branch of left coronary artery; and recent infarction of the posterolateral left ventricle (predominantly subendocardial) and interventricular septum.

CASE 5.*—

Gross Pathology: The heart weighed 580 grams. On the anterolateral surface of the left ventricle was an area 0.5 cm. in diameter of subepicardial hemorrhage. The subendocardial surface of the anterolateral wall of the left ventricle and the left ventricular surface of the interventricular septum showed a yellow-brown mottling. The left ventricular wall measured 1.5 cm., the right 0.6 cm. in thickness. On cut section an area 2 by 4 by 1 cm. in the anterolateral

*We are indebted to Dr. F. Anderson and Dr. W. Stern of the Genesee Hospital, Rochester, N. Y. for the pathological report of this patient.

left ventricle and septum was soft, yellow-brown, and surrounded by a thin hemorrhagic line. The majority of this was subendocardial except for one spot where it was transmural involving the epicardium in a 5 mm. area. There was a red-brown thrombus extending 1 cm. into the left anterior descending artery from its origin in the left coronary artery and completely occluding it. In the distal one-third of the circumflex branch of the left coronary artery was an old, white, hyalinized thrombus.

Microscopically (Fig. 1,*C*), there was a large irregular area of recently infarcted myocardium, showing polymorphonuclear leucocyte infiltration and loss of fibrillary markings. The muscle fibers stained deep pink with degenerated nuclei and "nuclear dust." Except in one small area, the subepicardial muscle fibers appeared normal, the infarcted area making up the inner two-thirds of the wall. Over the endocardial surface was an early organizing mural thrombus. A section from the left anterior descending coronary artery showed a thrombus with early fibroblastic activity. The estimated duration of the infarct was 4 to 7 days.

Anatomic Diagnoses: Thrombosis of the left anterior descending coronary artery with acute myocardial infarction (predominantly subendocardial); mural thrombus, left ventricle; and cardiac hypertrophy and dilatation.

CASE 6.—

Gross Pathology: The heart weighed 420 grams. The left ventricle was dilated. There was a large area of fibrous adhesion on the posterior surface of the epicardium. Both mitral and aortic valves showed considerable thickening. The thickness of the left ventricular wall measured 1.5 cm., and that of the right, 0.5 cm. Beneath the area of fibrous adhesions, however, the wall of the ventricle was thin and flabby and on section it appeared grayish-white in color and mottled with small pinkish areas. Section of the thicker part of the left ventricular wall and the interventricular septum showed a reddish-white cast to the subendocardial myocardium with small, sharply delineated, darker red areas. The ostia and lumen of both coronary arteries were obliterated.

Microscopically, two different types of myocardial change were noted. There were many dense, fibrous, hyalinized scars, some of which made up the great majority of the wall, others more scattered, but involving principally the subendocardial muscle. In these areas the endocardium was thickened and fibrous, and the adjacent muscle was hypertrophied and vacuolated. In one section there were numerous focal pale-staining areas of organizing injury consisting of new capillaries and early fibroblastic proliferation. The majority of these lesions occurred in the subendocardial area and in the trabeculae carnae. The estimated duration of the recent infarct was 4 to 8 days and that of the old infarcts 3 to 4 months.

Anatomic Diagnoses: Coronary arteriosclerosis with old coronary occlusion, recent myocardial infarction (subendocardial), and old myocardial scars.

CASE 7.—

Gross Pathology: The heart weighed 400 grams. The left ventricle was moderately dilated. There was moderate thickening of both mitral and tri-

cuspid valves. The orifices of both coronary arteries were narrowed by marked arteriosclerotic changes but no occlusion was demonstrated. The left ventricular wall measured 1.8 cm. in thickness, and the right, 0.4 cm. The subendocardial myocardium of the entire left ventricle was mottled yellowish-gray and there were superimposed irregular areas of pinkish-red granulation tissue. This process extended into the papillary muscle bundle and varied in thickness from 2 to 3 mm. in the lateral wall to almost the entire thickness of the myocardium in the anterior portion near the interventricular septum. However, it did not reach the epicardial surface in any area.

Microscopically, the subendocardial half of the left ventricular wall showed extensive areas of degenerating anuclear muscle, on the margins of which fibroblastic activity and new capillary formation were seen. This process also involved the trabeculae carnae. A section of papillary muscle showed a similar picture with some hyaline fibrous scarring. Areas of dense hyaline scarring were noted in the subendocardial area of the left ventricle. The estimated duration of the recent organizing infarct was 8 to 14 days.

Anatomic Diagnoses: Recent myocardial infarction (subendocardial), coronary arteriosclerosis, and cardic hypertrophy.

We wish to express our appreciation and thanks to Dr. Charles L. Yuile and Dr. Frank W. McKee for the pathological studies.

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THE DISCOVERY OF THE ORGANIC MERCURIAL DIURETICS

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IT WAS on October 7, 1919, that Johanna ——— was admitted to the First Medical University Clinic in Vienna, the Wenckebach Clinic. She was a patient with congenital syphilis with juvenile tabes, a young girl emaciated to skin and bones, with rigid and irregular pupils, and absent knee and ankle jerks. Because of recent vomiting, diarrhea, and increasing weakness, the family physician had been unable to continue her care at home and had asked his friend Dr. Paul Saxl to admit her to his service at the hospital.

It was not an "interesting case" as were most of the patients in this teaching hospital. The diagnosis was self-evident, treatment impossible. Her diarrhea was shared by almost everyone in starved post-war Austria. The only question was: What therapy would satisfy the referring practitioner and also enable us to most quickly discharge the patient? During rounds, Dr. Saxl asked me, a third-year medical student and the clinical clerk in charge of Johanna's case, to inject 1 c.c. of salicylate of mercury parenterally every other day.

The drug was unavailable on the ward and the charge nurse asked me to make out a prescription. With my Materia Medica still immature, I wrote out an order for a 10 per cent solution of mercury salicylate in water for hypodermic injection. No drug appeared within the next few days and Dr. Saxl inquired with increasing impatience why treatment had not yet been started. Finally, I called the pharmacy and learned, to my embarrassment, that the compound was insoluble in water and that they would require another prescription for a solution in oil. This, naturally, implied a delay of another few days.

While I was still at the phone, wondering how I could cover my blunder without evoking the wrath of my superior, a benefactor appeared in the person of a retired army surgeon. He was one of a group of former Austrian army surgeons who had suddenly been retired when the huge Austro-Hungarian army disintegrated, and who were trying to span the difficult transition to private practice. Many became onlookers at the Clinic, in hopes of gathering some knowledge of "civilian" medicine. The one in question was a friendly, elderly gentleman, named Raszowsky, I believe, who noticed my distress and to whom I revealed my misfortune. Producing a small box from his pocket he said: "I received this sample in the mail this morning; it's a new mercurial antisyphilitic, Novasurol. Maybe you can use it instead." And with a sad smile he added, "I have no patients, anyway."

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I promptly secured the permission to inject Novasurol every other day, and I began immediately. No one expected any therapeutic effect. Nor, for that matter, an effect of any sort.

At that time a great change in the nursing staff was under way. Prior to World War I our nurses had been, on the whole, not more than attendants or practical nurses. At the Wenckebach Clinic, however, a new generation of nurses was evolving, ambitious, inspired, with good educational backgrounds and training. Making beautiful charts was their pride, with everything recorded and listed in various colors. Urine was collected and measured daily on *all* patients, and blue columns of varying heights clearly indicated the twenty-four-hour production.

On the day of the first Novasurol injection, a tall column indicated that Johanna _____'s urine output had reached 1,200 c.c. as compared to the usual 200 to 500. This evoked my curiosity, but no further comment at that time. Following the second and third injections, however, when she voided 1,400 and 2,000 c.c., I excitedly mentioned it at rounds. My report produced a benevolent smile and a rather lengthy but unconvincing discussion of the wavelike rhythm of biologic functions.

When, after a lapse of four days, I started the injections again, the tall blue columns promptly reappeared. I believed no longer in coincidence and finally succeeded in arousing some puzzled attention. No one had any idea with what manner of phenomenon we were dealing. One mercurial compound, calomel, had been known for some time to be a rather unreliable and weak diuretic when taken by mouth, but mercury injections had been used previously without any diuretic effect. In a vague, unformed way, I entertained the concept that Novasurol somehow exerted a shocklike curative effect on the syphilitic kidney, allowing it to temporarily compensate for past deficiency.

As it happened, another syphilitic patient was on our ward at that time. He was a large man, a cab-driver, with syphilitic heart disease in advanced congestive failure. The customary diuretics no longer had any effect and his urinary output was extremely small. This, indeed, was the ideal case for the *experimentum crucis*.

After the injection of 2 c.c. of Novasurol intramuscularly, the patient passed a massive amount of almost colorless urine. The flow continued throughout the day and the night and by the next morning he had, to our amazement, eliminated over ten liters. We were convinced that we had witnessed the greatest man-made diuresis in history.

Now everyone became genuinely excited. Under a rather transparent blanket of secrecy, we scurried about in search of more patients on whom to test our discovery. We were repeatedly able to reproduce these miraculous results, causing deluges at will, to the mutual delight of the patients and ourselves.

The explanation behind the action of our diuretic marvel remained obscure. Some connection between the antisyphilitic effect of mercury and the phenomena observed was still foremost in our minds. We tested other forms of injectable mercury on our patients, with no results.

Soon afterward there was admitted to our wards a boy with a huge rheumatic heart and tricuspid insufficiency, in severe, water-logged failure, almost anuric and obviously terminal. The case seemed hopeless and he suffered cruelly. In sympathy and desperation, we tried our wonder drug. He received his injection and, unfortunately, expired the following day. Before his death, however, he passed three liters of urine. Post-mortem examination confirmed the clinical diagnosis and revealed no evidence of syphilis.

It became apparent that we were dealing with a potent diuretic which was independent of antisyphilitic activity and vastly superior to any diuretic thus far used. I personally was not greatly impressed, believing, from my textbook knowledge, that we had merely added another diuretic to the already long and (at least in the pharmacology texts) impressive list which extended from infusions of sarsaparilla to urea and Diuretin.

In January, 1920, I left on a pre-arranged trip to Berlin to continue my studies there as a guest in a friend's home. In my absence, Dr. Saxl and Robert Heilig, my successor to the ward, continued the feverish investigation. Knowing very little about renal physiology—Cushny's, Richard's and Homer Smith's works were still forthcoming—an enormous amount of diligent but fruitless labor was put into the study of a supposed extrarenal mechanism of mercurial diuresis.

As if by an act of providence, no untoward effects of the injections were observed until the discovery was made public in Vienna. Immediately afterwards, a series of severe mercury intoxications occurred, including fatal hemorrhagic colitis. If these had developed in our initial patients, it is doubtful whether the series would have been continued, or Novasurol ever been recommended as a diuretic.

This is the story of how a series of fortunate errors and coincidences resulted in "a discovery that has completely revolutionized the treatment of congestive heart failure" (Willius and Dry[4]). The main credit should probably be given to the diligent nurse who, without specific orders, faithfully collected and charted the daily urine output. We may perhaps take pride in having taken note of an occurrence which had undoubtedly annoyed numerous patients who had received Novasurol injections in the preceding seven years (and whose complaints about polyuria were probably lightly dismissed by the physicians). It should be remembered that our first patient was not edematous, either, and probably, if anything, dehydrated.

Not until fifteen years after the general introduction of the mercurials as diuretics was progress in the physiology of the kidney able to clarify the mechanism by which Johanna _____, to our surprise, had parted with her body fluids following the injection of Novasurol.

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CARDIAC ARRHYTHMIAS IN MYOCARDIAL INFARCTION

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THIS study was undertaken to see if any correlation exists between the location of a myocardial infarction and a resulting arrhythmia. It is generally agreed that complete heart block following myocardial infarction is practically always associated with posterior infarction. However, there are conflicting reports on the association of the other arrhythmias with either anterior, posterior, or lateral infarction. Master and his co-workers[1] (1937) in an analysis of 300 cases concluded that with the exception of complete heart block there is no correlation between the exact site of thrombosis or infarction and the type of arrhythmia. Master and his co-workers[2] (1938) reviewing 375 cases of coronary occlusion noted that 11 of 12 cases of complete or partial heart block were associated with posterior infarction. Wood, Wolferth, and Bellet[3] (1938) reported a high incidence of auricular fibrillation in association with lateral wall infarction. Thomson and Feil[4] (1944) confirmed the above by reporting an incidence of 5 cases of fibrillation (or flutter) in 9 patients with lateral wall infarction. However, a review of these case reports shows that 3 of the 5 had autopsy and/or electrocardiographic evidence of posterior infarction in addition to the lateral wall involvement. However, Mintz and Katz[7] (1947), Rosenbaum and Levine[6] (1941), and Billings and his associates[8] (1949) noted no correlation between auricular fibrillation and the location of the infarct. Rosenbaum and Levine did note that 20 out of 29 cases of complete or partial heart block did have posterior myocardial infarction (although in an earlier study on only 7 cases of partial and/or complete heart block, 4 were associated with posterior and 3 with anterior infarctions).

This report includes 127 cases of acute myocardial infarction, 73 of which were anterior and 54 posterior in location. The diagnosis of the location was based on definite electrocardiographic evidence and/or autopsy findings. All arrhythmias were proved electrocardiographically (using 12 leads routinely). Ventricular ectopic beats were not included in this study.

Posterior Infarction.—Of the 54 patients, 13 (24.1 per cent) developed arrhythmias:

Complete auriculoventricular dissociation (with periods of partial heart block)	2
Partial (second degree) heart block	2
First degree heart block (PR = 0.28 second)	1
Transient right bundle branch block	1

From the Oakland Veterans Administration Hospital, Oakland, Calif.

Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are a result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Auricular flutter	3
Auricular fibrillation	1
Auricular bigeminy	1
Coronary sinus rhythm	1
Auriculoventricular nodal rhythm (with auricular standstill)	1

Anterior Infarction.—Of these 73 patients, only 2 (2.7 per cent) developed an arrhythmia:

Auricular fibrillation	1
Transient left bundle branch block	1

Mortality.—

Average mortality of all patients = 25/127 or 19.6 per cent.

Average mortality of patients with anterior infarcts = 16/73 or 21.9 per cent.

Average mortality of patients with posterior infarcts = 9/54 or 16.7 per cent.

Average mortality of patients with posterior infarcts without arrhythmia = 5/41 or 12.2 per cent.

Average mortality of patients with posterior infarcts with arrhythmia = 4/13 or 30.8 per cent.

Of the four deaths in the group of posterior infarction with arrhythmias, one died while in complete heart block, one died after the auricular fibrillation had converted to a regular sinus rhythm, one died with a first degree heart block, and one died with a coronary sinus rhythm. In the remaining patients with arrhythmia who survived, the arrhythmia converted to a regular sinus within a few days.

DISCUSSION

The auriculoventricular node is situated in the upper posterior portion of the interventricular septum. In 92 per cent of hearts[9] the blood supply to this region is the right coronary artery through its branch, the ramus septi fibrosi, the specific artery to the auriculoventricular node. In 60 per cent of hearts the auricles and sinoauricular node are supplied by the right coronary artery. It would therefore be expected that posterior infarction (resulting from occlusion of the right coronary artery) would result in a high incidence of disturbance in auriculoventricular conduction (first, second, and third degree heart block) and in other forms of auricular and nodal arrhythmias. This is borne out in the above study.

SUMMARY AND CONCLUSIONS

1. Posterior infarction is associated with a high incidence of auricular and nodal arrhythmias (24.1 per cent in comparison with anterior infarction (2.7 per cent).

2. The presence of an associated arrhythmia, especially if persistent, is of grave prognostic significance.

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COR BIATRIATUM TRILOCULARE

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BROOKLYN, N. Y.

COMPLETE absence of the ventricular septum, resulting in a three-chambered heart, is a rare cardiac anomaly. In Abbott's analysis of 1,000 cases of congenital cardiac disease, thirteen cases were reported in which cor biatriatum triloculare was the primary lesion. In fourteen additional cases it was found complicating other defects, making the total incidence 2.7 per cent of the total series.[1]

This rare condition was recently observed in a newborn infant who died four days after birth. The case is reported because of the interesting electrocardiographic findings, particularly in the multiple unipolar chest leads, which were correlated with the anatomic findings at autopsy.

CASE REPORT

M. A., a girl aged 3 days, had been delivered at the Beth-El Hospital, Brooklyn, N. Y., May 30, 1949.

Family History: The mother and father were both 24 years old and in good health. One brother, 18 months old, was living and well. Mother was para i, gravida ii. The last pregnancy had been uneventful and no disturbance of the fetal heartbeat was observed. There had been no acute infections. Delivery was performed under caudal anesthesia, with low forceps. The position of the fetus was left occipitoanterior; the total duration of labor was six hours and twenty minutes. Labor was normal in every respect. The blood Wassermann was negative, the blood was Rh positive, and the blood type was O.

Clinical History: The baby was born at full term in good condition; the weight was 6 pounds, 2 ounces, length 19 inches; no abnormalities were noted. The infant was apparently healthy, took feedings well, and cried lustily. On June 2, three days after birth, about noon time, some dyspnea and cyanosis were noted. Thereafter the condition rapidly deteriorated.

Physical examination showed a normal female infant in apparent respiratory distress. She was cold and cyanotic; the temperature was 95° F. The fontanels were bulging. There were diminished breath sounds in both lung fields. Cardiac examination disclosed tachycardia (approximately 180 per minute), and heart sounds of poor quality; no murmurs were heard. The liver was palpable about two and one-half fingerbreaths below the costal margin; the spleen was not felt.

The blood count disclosed the following: 6.2 million erythrocytes, hemoglobin 18.6 Gm., 14,000 leucocytes with segmented polymorphonuclear cells, 59 per cent; lymphocytes, 28 per cent; staff cells, 5 per cent; monocytes, 5 per cent; and eosinophiles, 3 per cent.

A teleroentgenogram was technically imperfect and accurate interpretation was not possible.

An electrocardiogram was taken, including standard and unipolar extremity and circumferential precordial leads. A detailed analysis of the record is presented hereafter. The pertinent findings were unusual axis deviation with evidence of marked clockwise rotation of the heart.

From the Cardiographic Laboratory, The Mount Sinai Hospital, New York, N. Y., and The Pediatric Service, The Beth-El Hospital, Brooklyn, N. Y.

The highest temperature recorded was 97° F. The patient was kept warm and oxygen, penicillin, and vitamin K were administered. Tracheal aspiration was performed periodically. The infant died on June 3, 1949, four days after birth.

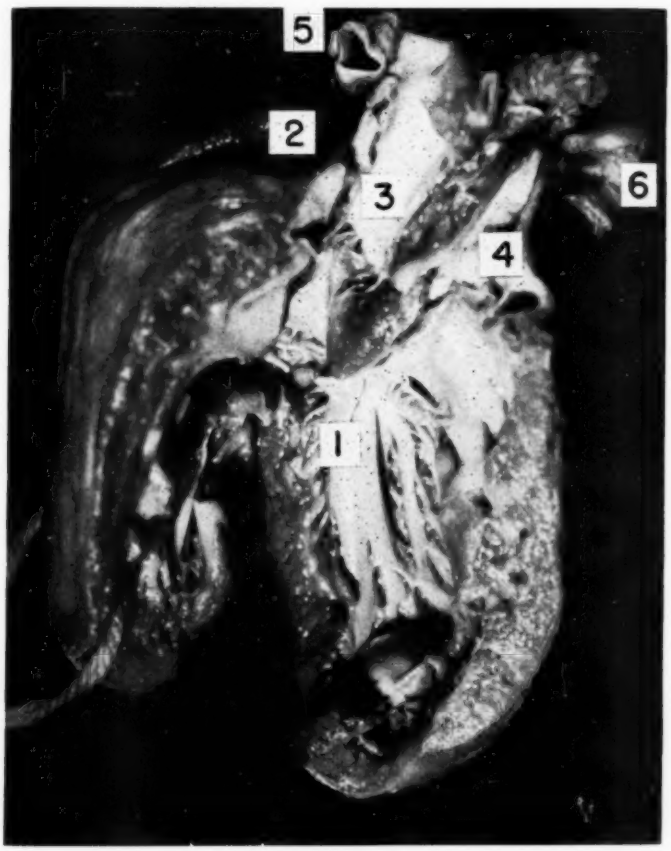

Fig. 1.—The dissected heart in a case of cor biatriatum triloculare. *1*, common ventricle; *2*, appendage of left atrium; *3*, aorta (transposed); *4*, pulmonary artery; *5*, superior vena cava; and *6*, ductus arteriosus.

*Pertinent Observations at Necropsy:** The body was that of a full-term female infant, well developed, well nourished; the weight was 2,893 grams. All the organs were in their normal positions. Both diaphragms reached the fifth intercostal space. Both lungs were markedly congested and hemorrhagic, and there were some areas of collapse. The heart weighed 23.5 grams, and was softer in consistency than usual. The right atrium was large and the superior and inferior venae cavae entered the chamber in a normal fashion. The interatrial septum was thin and a large defect was present. The left atrium was very small, had a long, tapering atrial appendage, and received the pulmonary veins normally. Only one large ventricular cavity was present with no evidence of any septum except for a very small rudimentary ridge separating the aorta from the pulmonary artery. The ventricular wall measured 3 mm. in thickness. Both great vessels were well developed, transposed, and a patent ductus arteriosus was present. The aortic and pulmonary valves were thin, delicate, and competent. The mitral and tricuspid

*Necropsy performed by Dr. Nathan Mitchell.

valves were rudimentary and incompetent. The coronary arteries were normal in origin. The liver was of normal size, shape, consistency and weighed 128 grams. The brain weighed 330 grams. There was an area of about 3 cm. presenting a subarachnoid hemorrhage, covering the right cerebellum, pons, and midbrain. The anatomic diagnosis was cor biatriatum triloculare, interatrial septal defect, patent ductus arteriosus, and subarachnoid hemorrhage.

Fig. 2.—View of the right atrium. Probe passed through the defective interatrial septum.

Electrocardiographic Findings: The electrocardiogram was obtained on June 2, 1949. The record included the three standard leads (I, II, and III) the three augmented unipolar extremity leads (aV_R, aV_L, aV_F) and fifteen unipolar chest leads (V-9 to V + 9), as described by Kisch and Richman.[2] The chest lead positions, were as follows: V_1—exploring electrode in the midsternal line at the level of the fourth intercostal space. V + 2—same as V_1, but exploring electrode in the left parasternal line. V + 3—not taken for technical reasons. V + 4—exploring electrode in the fifth left intercostal space at the midclavicular line. V + 5 to V + 9—exploring electrode at the same level as V + 4 at the left anterior axillary line, midaxillary line, posterior axillary line, angle of the scapula and left paravertebral line, respectively. The corresponding chest leads on the right side were designated as V-2, V-3, etc. Lead I was taken synchronously with the chest leads as a reference tracing.

The electrocardiogram (Fig. 4) disclosed regular sinus tachycardia with a rate of 160 per minute. The standard leads showed an unusual axis deviation characterized by deep S waves in all the three leads. The unipolar extremity leads revealed a left ventricular pattern (qRs) in the left arm and a right ventricular pattern (rS) in the left foot. The right arm lead (aV_R)

showed a qR and inverted T, a pattern commonly seen when the electrode faces the back of the left ventricle. The precordial leads showed a right ventricular pattern (rS) from V-7 to V + 6 and a left ventricular pattern (qr) in + 8 to − 8. In positions + 8 and + 9 the q deflection was synchronous with the R wave in Lead I whereas in positions −9 and −8 it actually followed it

Fig. 3.—View of the left atrium showing appendage, large atrioventricular, and smaller interatrial, openings.

rather than preceded it as would be expected in a normal Q wave. In V-7 a small R wave appeared before the so-called Q wave and progressed in size up to position I where it merged with the R, succeeding the Q wave, resulting in one R. These "q" waves, as shown by Kisch and Richman,[3] are composed of the S of the right ventricle and the q of the left ventricle, and the upstroke which in −7 appears before this q is the R of the right ventricle. Thus, proceeding from the right side to the middle of the chest, the R of the right ventricle grows progressively larger and the second upstroke following the S, representing the R of the left ventricle disappears gradually. The electrocardiogram is thus predominantly of the right ventricular pattern with marked clockwise rotation.

DISCUSSION

Cor biatriatum triloculare is regarded as the result of an extremely early arrest in the development of the heart. During development of the fetus, the

primitive cardiac tube bulges forward and swings to the right; the anterior portion forms the bulbus cordis and the posterior part of the loop forms the common ventricle. Normally the ridge which separates the bulbus cordis from the common ventricle atrophies and, coincidentally, the ridge of the aortic septum develops. The anterior portion of the bulbus cordis develops into the outflow tract of the right ventricle.[4] An arrest in the development of the heart at this stage will result in the anomaly under discussion.

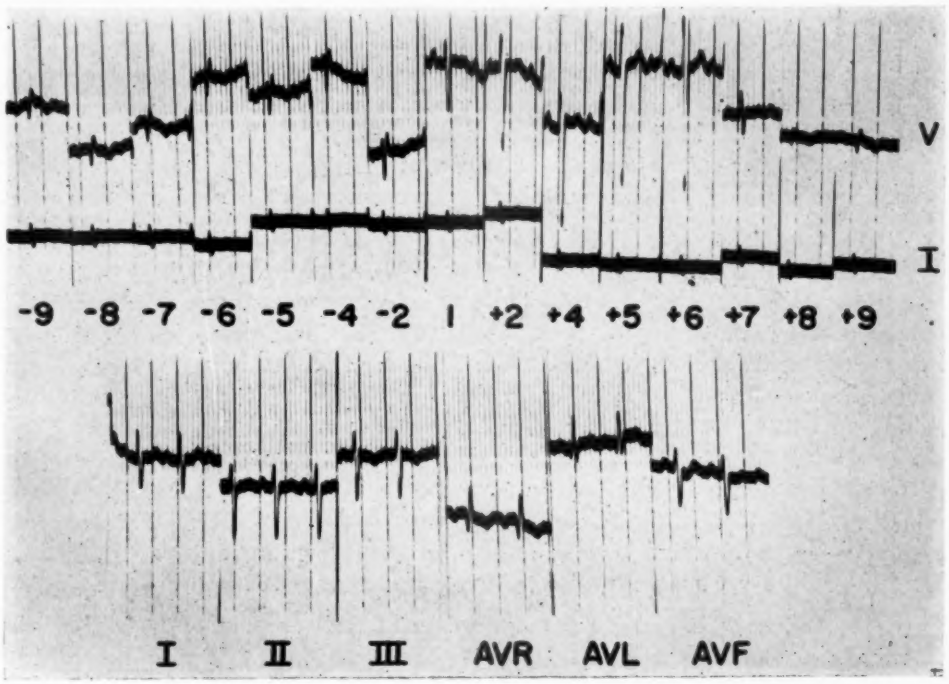

Fig. 4.—An electrocardiogram showing regular sinus tachycardia with a rate of 160 per minute. For further discussion see text.

The essential feature of this malformation is a single ventricle with no evidence of a septum separating left from right ventricle. Two atria are present. The common ventricle thus receives blood from both atria and empties into the aorta and pulmonary artery. The arrest in the development of the ventricles may or may not be associated with malformation of the atrial septum. If the interatrial septum develops normally a cor biatriatum triloculare will result. On the other hand, if there is complete arrest in the development of the atrial septum it will result in a cor biloculare. There may also be variations in septal development resulting in deficient separation of the two atria. In the condition under discussion, the left atrium is simply a small appendage communicating with the normal right atrium through a large interatrial septal defect. The rudimentary mitral and tricuspid valves open into the common ventricle.

The presence or absence of cyanosis depends upon the volume of blood which reaches the lung. In this case the pulmonary artery was dextroposed and well

developed. Thus a large volume of oxygenated blood from the lungs reached the systemic circulation through the aorta, resulting in little cyanosis, despite the fact that the aorta contained mixed venous and arterial blood. Cyanosis appeared only after the cerebral hemorrhage occurred.

The electrocardiogram, according to current knowledge, represents the resultant graphic expression of the different electrical potentials of the atria, interventricular septum, and ventricles. For example, the Q wave in the levocardiogram has been attributed to the stimulation of the left bundle branch before the right, thus producing early activation of the left side of the interventricular septum, resulting in a small negative deflection (q) followed by an R wave (qR pattern). The dextrocardiogram is characterized by a small R and deep S wave. In pathological conditions, where an interruption or a delay in conduction through one of the bundle branches is present, as in right or left bundle branch block, a characteristic electrocardiographic pattern is observed.

In the present case, the chest leads showed a left ventricular pattern (qr) on the extreme right (V-9 and V-8) and extreme left side of the chest posteriorly (V+8 to V+9). A right ventricular pattern (rS) was present over the entire anterior aspect of the chest (V−7 to V+6). The left ventricular deflections (qR) were small as compared with the right ventricular deflections (rS) which were of large size and present almost through the entire chest. This pattern is commonly observed in the electrocardiograms of normal newborn infants.[5] In older children, as reported by Master, Dack, and Jaffe,[6,7] the qR pattern of the left ventricle is more prominent and may extend anteriorly into the left axilla (V_6) but, otherwise, is similar to the above. In the univentricular heart of the fish and frog, as reported by Kisch,[8] the electrocardiograms taken from different points of the heart show a typical dextrogram (rS) and a levogram (qRs).

A comparison of the electrocardiogram in the case under discussion with the findings in the univentricular heart of the fish and frog, and with the findings in the chest leads of normal children shows no essential differences. Actually, the electrocardiogram in our case resembles that of a normal infant except that there is evidence of rotation of the electrical axis. In the univentricular heart a characteristic levo-and dextrocardiogram is present despite the absence of an interventricular septum or bundle branches. In view of this, the findings of Glomset, Glomset, and Birge,[9-13] may be of significance. These investigators doubt the actual existence of a conduction system in man. From their review of the literature, as well as from their own investigation of the conduction system in ungulates, in the dog, and in man, they came to the following conclusion: The bundle of His is a slender muscle bundle measuring 1 to 2 mm. in diameter, does not bifurcate, is not covered by a special connective tissue, and is structurally identical with other muscle fasciculi of the heart.. No muscle connection was found between the fibers of the bundle of His and those of the right atrium. There was no evidence of a special blood supply. There was no anatomic evidence to support the myogenic theory of cardiac conduction. These investigators found an extremely well-developed intrinsic nervous system of the heart consisting of nerve cells, trunks, networks of nerve fibers and ganglia, most preva-

lent in the atria and the atrioventricular groove. It was concluded that the cardiac musculature is under nervous control similar to that of other muscular tissues.

Kisch,[8] in his studies of the fish and frog heart, concluded that the levo- and dextrocardiograms are influenced by potentials produced by the different muscles adjacent to the electrode and not by a conduction system.

If the above findings in the human and the animal heart are corroborated by further investigation, our present concept of the origin and propagation of the cardiac impulse, as well as its expression in the electrocardiogram, will have to be modified.

SUMMARY

A case of a univentricular heart has been presented (cor biatriatum triloculare), with complete absence of the interventricular septum. Despite the latter finding, multiple chest leads revealed a typical dextro- and levocardiogram on the anterior and posterior sides of the chest, respectively. The significance of this observation in an evaluation of theories of intraventricular conduction is discussed.

I wish to express my appreciation to Dr. A. M. Master, Dr. S. Dack, and Dr. N. Mitchell for their assistance in the preparation of this paper.

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Clinical Reports

THYROTOXICOSIS FACTITIA MASKED AS HEART DISEASE

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THE diagnosis of factitious hyperthyroidism, that is, hyperthyroidism due to the ingestion of thyroid substance, has been extremely difficult in the past when the thyroid has been taken secretly and the fact concealed from the examining physician. It should be suspected in any patient with typical signs of an overactive thyroid, absence of a palpable thyroid gland, and poor response to adequate therapy, although all of these may occur in endogenous hyperthyroidism. In so-called masked hyperthyroidism, that is, hyperthyroidism manifested by a single symptom or by symptoms restricted to a single system, diagnosis presents further problems. This case is presented because it represents concealed factitious hyperthyroidism masked as heart disease, the first case of this type to be reported, so far as we have been able to determine.

The patient was a male cook aged 53 years. He complained of palpitation of seven weeks' duration.

There was no previous history of cardiac symptoms, other than episodes of dizziness and weakness during the past two years. At these times he experienced dizziness and a sensation of faintness, "blacking out," but no loss of consciousness. Physicians whom he consulted ascribed this to low blood pressure; he was told that the systolic varied between 90 and 120 mm. Hg. He had electrocardiographic studies which were considered to be normal. There was no history of chest pain, dyspnea, or of any manifestation of rheumatic fever. Twenty years and again five years prior to admission he had a typical syndrome of pain relieved by food, and a duodenal ulcer was demonstrated by x-ray. For the past five years he had vague right upper quadrant distress unrelated to food; he had done nothing to secure relief. He always had a fried and fatty food intolerance which produced "gas and sour stomach." For three months he had infrequent attacks of watery diarrhea without cramps or gross blood. He did not use tobacco or alcohol, and his consumption of tea and coffee was moderate.

About seven weeks before admission he noted the onset of sudden palpitation. This persisted until the time of entry to the hospital. Upon questioning he admitted to a vague, poorly localized, uncomfortable feeling in the chest. He also felt somewhat dizzy. At the time of onset he consulted a physician and a cardiologist who prescribed quinidine, 0.2 Gm. three times daily, and a short while later small irregular doses of digitalis in addition. There was no response, and he consulted a second cardiologist, who prescribed quinidine, 0.2 Gm. every two hours and later, every three hours. In addition, he took phenobarbital, but denied other medication of any sort. No treatment gave relief, and he was referred to the hospital for study and therapy.

After the diagnosis had been established by methods to be described, the following additional history was obtained from the patient's wife, and confirmed by the patient with some diffidence.

From the first medical (Dr. George Baehr) service of The Mount Sinai Hospital, New York.
*Fellow in Cardiology.
†Sarah Welt fellow in Medicine.

Three months prior to hospitalization the patient was given thyroid to reduce his weight. The original prescription called for thyroid, 150 mg. with phenobarbital, 15 mg. to be taken three times daily. This was subsequently doubled by the patient and still later, dissatisfied with the response, he increased his dosage from the prescribed three capsules per day to eight capsules per day. At this time he was therefore consuming 1.3 Gm. (20 gr.) of thyroid each day. He continued this medication until two or three days before he entered the hospital.

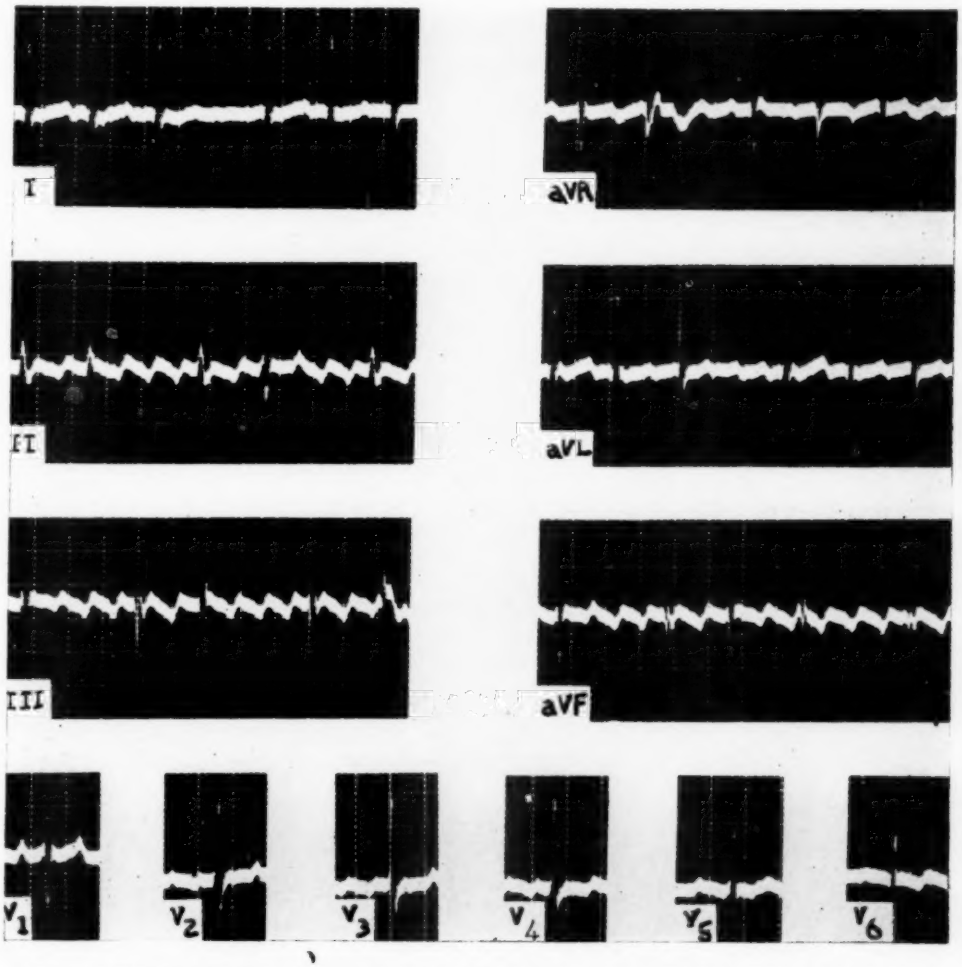

Fig. 1.—Electrocardiogram, Aug. 24, 1949. Auricular flutter with varying degrees of A-V block.

On admission, physical examination revealed a well-built, moderately obese man lying comfortably in bed. He was afebrile. Examination of the head, including fundoscopy, was normal. The trachea was in the midline, the thyroid was not palpable, and there was no lymphadenopathy. The cervical veins were not distended, but flutter waves were readily discernible. The lungs were clear and respiration was normal. The heart was not enlarged. No thrill was palpable; there was no murmur. The heart sounds were faint. A_2 equalled P_2. The cardiac rhythm was generally irregular, but was interspersed with cycles of from four to twelve beats of apparent regularity. The apical rate was 120. The radial pulses were equal, synchronous, and irregular, with a rate of 80. The peripheral pulses were of good quality. Blood pressure was 112/74 mm. Hg.

The liver edge was just palpable on deep inspiration. There was no hepatojugular reflux. Flutter waves could be seen transmitted from the liver to the anterior abdominal wall. Examination of the abdomen was otherwise negative. The prostate gland was symmetrically enlarged to a moderate degree. There was no cyanosis, clubbing, edema, or tremor. The skin was dry. Neurologic examination revealed no abnormality.

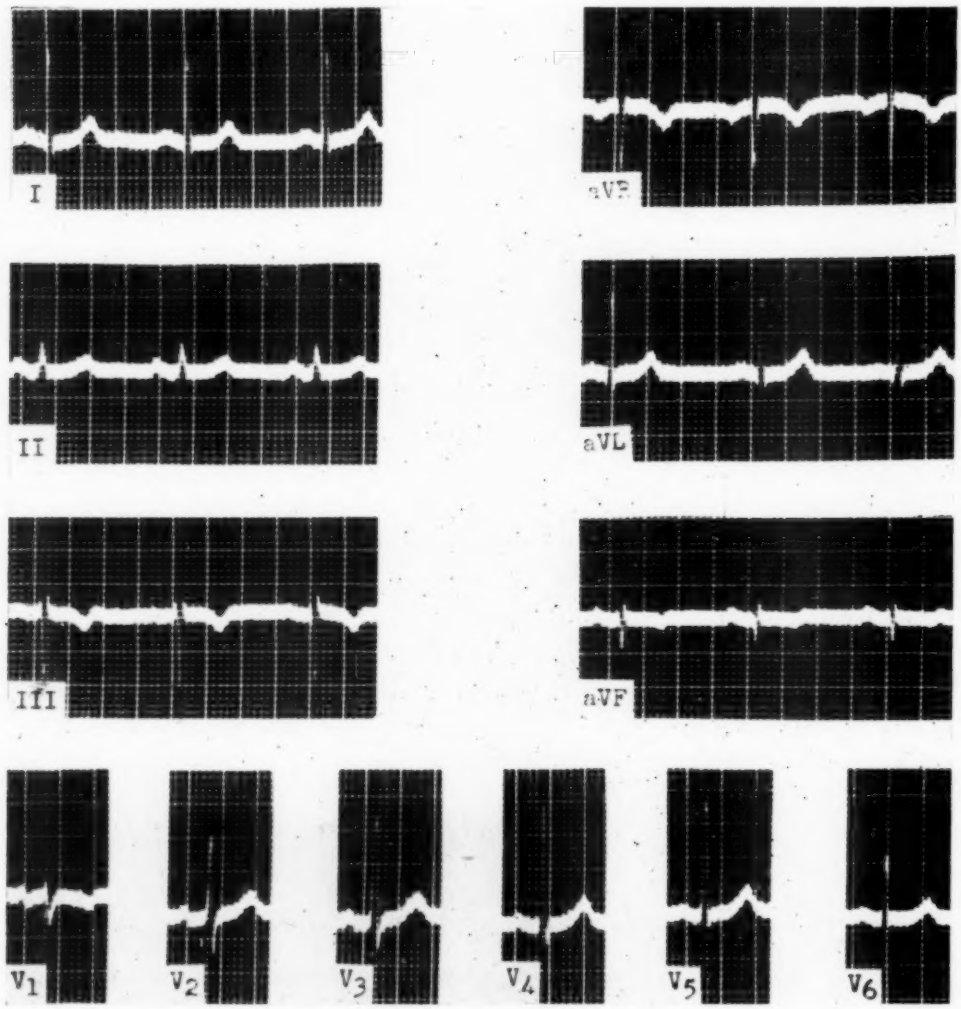

Fig. 2.—Electrocardiogram, Sept. 20, 1949. Normal sinus rhythm, left axis deviation, no abnormality.

The hemoglobin was 15.5 Gm. per cent. The white blood count was 6,850 cells per c. mm. with a normal differential. Erythrocyte sedimentation rate was 10 mm. per hour (Westegren). Blood Wassermann was negative. The blood urea nitrogen was 15 mg. per cent; fasting blood sugar, 100 mg. per cent; serum cholesterol, 330 mg. per cent; alkaline phosphatase, 9 K.A. units; total protein, 6 Gm. per cent; thymol turbidity and cephalin flocculation, negative; serum chlorides, 602 mg. per cent.

An attempt was made to discover the cause of the arrhythmia. Arm to tongue circulation time (calcium gluconate) was 17 seconds. Venous pressure was 30 mm. of water with no rise on right upper quadrant pressure. An electrocardiogram taken on admission, showed auricular flutter with varying degrees of block; but later in his course he was usually found to have 4:1 block (Fig. 1). X-ray examination of the chest showed the heart to be normal in size and configuration. Two basal metabolic rate determinations were minus 12 per cent and minus 14 per cent. An oral cholecystogram was within normal limits.

On the second hospital day he was given a tracer dose of 100 uc of radioactive iodine, I^{131}. Of this he excreted 81 per cent within twenty-four hours. This high value is consistent with the diagnosis either of myxedema or of factitious thyrotoxicosis; and in the presence of auricular flutter of unestablished etiology the latter was thought to be more likely. Two days later, before serum iodine was studied, Priodax, (beta-(4-hydroxy-3,5-diiodophenyl)alpha phenylpropionic acid), was administered for cholecystography. Plasma protein-bound iodine was reported as 56 gamma per cent (normal, 4 to 8 gamma per cent). However, this determination was made three days after the patient had taken Priodax, and therefore it has no diagnostic significance. Four days later a second radioactive iodine study showed only 41 per cent excretion in twenty-four hours. This is normal.

On the following day it was decided to attempt to convert the arrhythmia to a normal rhythm in spite of a ventricular rate which had dropped to 80, and despite the absence of congestive failure. The patient was given 0.3 mg. of acetyl-strophanthin by vein without effect. This was followed in a short time by 0.3 mg. of strophanthin K by vein, again without effect. That evening he was given 0.8 mg. of digitoxin by mouth, and the following morning 0.4 mg. The auricular flutter persisted. It was then decided to change to oral Digoxin and to administer it to the point of toxicity. He was given 1.5 mg. daily for two days, at which time he complained of anorexia. The dosage of Digoxin was reduced to 1.0 mg. daily, which he received for two days, but with persistence of anorexia and development of slight nausea. The dose was further reduced to 0.5 mg., and on this day the rhythm changed to normal sinus rhythm. The electrocardiogram showed R-ST depressions and low voltage T waves. These changes were attributed to digitalis and disappeared with the discontinuance of the medication (Fig. 2). In view of the etiology, it is possible that the restoration to normal rhythm was spontaneous rather than directly related to the cardiotherapy.

The patient was discharged from the hospital without medication and with instructions to avoid thyroid. In six months of observation there has been no recurrence of palpitation, auricular flutter, or development of any other cardiac abnormality. Blood iodine determination three months after discharge was 7.4 gamma per cent. Radioiodine excretion was 34 per cent in twenty-four hours. Both of these values are normal.

It is remarkable that despite the widespread use of desiccated thyroid for such ill-defined conditions as easy fatiguability, mild anemia, depressed states, menstrual irregularities, infertility, narcolepsy, and obesity with or without hypometabolism, published reports of factitious hyperthyroidism are relatively few in number. Nevertheless, as many as twelve cases of concealed exogenous hyperthyroidism have been seen by a single observer in one clinic.[1]

The cases of factitious hyperthyroidism which have been found in the literature fall into three categories. The most obvious is the overt type with well-developed signs and symptoms of hyperthyroidism and a history of thyroid ingestion.[2-8]

The second group comprises those patients with clear-cut signs of hyperthyroidism where, for one reason or another, the patient conceals the fact that he is taking thyroid medication.[9-12] These patients suffering from concealed exogenous hyperthyroidism have occasionally been so unfortunate as to undergo definitive surgical operation under the impression that they were suffering from classical Graves' disease. In eight cases of induced hyperthyroidism which we

have seen in the past two years, three were of the concealed type. One of these patients was admitted for operation before the diagnosis was established by radioactive iodine and plasma iodine determinations.

As far as we know, no cases have heretofore been reported of a third type, masked concealed factitious hyperthyroidism.

Most instances of endogenous hyperthyroidism which are masked as heart disease are associated with auricular fibrillation. In general, auricular fibrillation occurs in 5.8 to 34 per cent of hyperthyroid patients,[13-18] hyperthyroidism in 3.5 to 14 per cent of all patients with auricular fibrillation.[19-23] Auricular flutter has been described in 1.5 to 5.5 per cent of hyperthyroid patients;[17,24-27] hyperthyroidism in 6 to 25 per cent of all cases of auricular flutter.[19,28,29] We have found only one report of a case of masked hyperthyroidism manifested as auricular flutter.[30]

From the foregoing it is clear that thyroid stimulation should be suspected in all cases of auricular fibrillation or flutter. The diagnosis may be confirmed by study of the basal metabolism, plasma protein-bound iodine, and excretion or uptake of radioactive iodine. In endogenous hyperthyroidism, the basal metabolic rate is usually elevated, the plasma protein-bound iodine is elevated,[31] the urinary excretion of radioactive iodine is low, and the uptake by the thyroid gland is high.[32] The same methods of diagnosis may be applied to factitious hyperthyroidism. However, in these cases, while the basal metabolism and the plasma protein-bound iodine are similar to the former group,[33] the urinary excretion of radioactive iodine is also high (over 80 per cent) while the uptake is depressed.[9,34] In addition, the urinary excretion of total iodine is considerably elevated above that seen in either euthyroid or spontaneous hyperthyroidisms.[11,12]

Other conditions which may give a laboratory picture of iodine metabolism identical with that found in factitious hyperthyroidism are partial remission of hyperthyroidism due to the use of thio-uracil, the administration of iodine containing dyes for radiography, and some cases of acute thyroiditis.[35] These conditions should not present difficulties in differential diagnosis.

It is unfortunate that in this case a cholecystogram was made invalidating the results of the plasma protein-bound iodine determinations. Despite the cholecystogram, which was performed between the first two studies with radioactive iodine, the I^{131} excretion was considerably lower in the second test. This implies that the patient's thyroid gland was more depressed in function by the previously administered desiccated thyroid than by the subsequent Priodax. The low basal metabolic rate after discontinuance of medication, as seen in our patient, has been described as a sequela of thyroid administration by Riggs and associates.[33] It is probably two-fold in origin: due to depression of production of pituitary thyrotropic hormone and to saturation of the thyroid gland and blood stream with the iodine contained in the administered thyroid substance.

SUMMARY

A case of concealed factitious hyperthyroidism is presented, which was masked as heart disease manifested by auricular flutter and was diagnosed by the elevated radioiodine excretion.

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DIGITALIS INTOXICATION

Chronic Effects Manifested by Diarrhea and Auricular Flutter

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DIARRHEA is seldom so predominant a manifestation of digitalis intoxication that a patient is first investigated for primary gastrointestinal disease. In addition, it is not likely that that patient is suspected of auricular flutter if his heart is beating at a normal rate with a regular rhythm. This case is reported, therefore, because it shows these unusual presenting indications of chronic digitalis intoxication.

CASE REPORT

A 59-year-old salesman presented himself on Feb. 10, 1942 with a chief complaint of diarrhea for two weeks. The onset was sudden with abdominal cramps, intermittent in character, followed by frequent brown, watery, bowel movements. These increased until he was having four to six daily evacuations of mushy stool. There had been loss of appetite for about two weeks, but no dietary indiscretion, vomiting, or fever. He claimed to have lost ten pounds in the past three months. He gave no history of previous illness or drug therapy. He had not been to a doctor for the past five years.

Physical examination revealed a middle-aged, well-nourished white man in no acute distress. The temperature was 99° F.; the pulse 84; the blood pressure 138 mm. Hg systolic, and 74 diastolic. The tongue was clean and moist. There were no cervical arterial pulsations or venous engorgement. The heart was not enlarged to percussion or auscultation. The cardiac sounds were of good quality; the aortic second sound was louder than the pulmonic. There was a soft, apical systolic murmur transmitted toward the axilla and a harsh nontransmitted systolic murmur over the aortic area. The rhythm was regular. The lungs were clear to percussion and auscultation. The liver was not enlarged; there was no peripheral edema or cyanosis. On rectal examination, the skin about the anus was reddened but not excoriated; no abnormal masses were felt; no blood or tarry stool was found on the examining finger.

Roentgen-ray examination of the heart and lungs showed a slight prominence of the pulmonary conus. The arch of the aorta was elongated and tortuous. The pulmonary markings were accentuated; the lung fields were otherwise clear. Barium meal and enema revealed no intrinsic lesions of the gastrointestinal tract. Sigmoidoscopic examination was negative, as were stool examinations for ova, parasites, and blood. Estimations of blood urea and sugar were within normal limits; the blood Wassermann was negative, the urine analysis showed no abnormalities. The galactose tolerance, hippuric acid tests, and estimation of total blood cholesterol and esters showed no impairment of liver function.

On February 12, he began to vomit and soon was unable to retain anything by mouth. At this point he became concerned because he was unable to take his "tonic." Upon investigation the tonic was found to be brownish tablets he had been taking twice a day for five years. Since he did not consider this a drug, he had not thought to mention it before. The tablets had been prescribed for him by his previous physician, whom he had seen last five years ago. This physician could not be located, but the pharmacist who made up the prescription was questioned. He

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reported that the tablets were digitalis leaf, grains 1½, and that the patient had had the prescription refilled on numerous occasions over the past five years.

As soon as this additional information was received, an electrocardiogram was taken (Fig. 1, February 12).

It showed an auricular flutter with "P" waves occurring at the rate of 264 per minute, and ventricular complexes occurring from 66 to 88 per minute. The RS-T junctions and T waves were depressed in all leads. Two days after stopping the drug, the vomiting had ceased, and the diarrhea was somewhat diminished. Parenteral fluids were stopped.

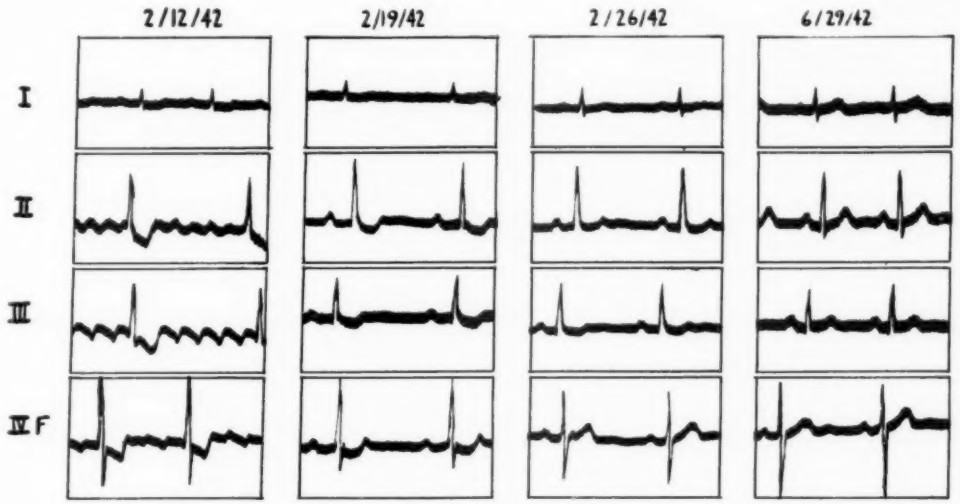

Fig. 1.—For description, see text.

One week later (February 19) his appetite returned and he was having one formed stool a day. His temperature, pulse, and respiratory rates were within normal limits and he was asymptomatic. The electrocardiogram on February 19 (Fig. 1) showed a regular sinus rhythm with a first degree auriculoventricular block. The rate was 54; the P-R interval 0.28 second. The RS-T junctions were less depressed than those of the tracing on February 12 and the T waves were beginning to become upright.

After another week (February 26) the electrocardiogram showed a P-R interval of 0.22 second, the T waves were more upright and the RS-T depressions had almost completely disappeared. In June, four months after digitalis was stopped, the patient was seen again. He had been and was in good health. The electrocardiogram at this time, June 19 (Fig. 1) was within normal limits.

DISCUSSION

Anorexia, nausea and vomiting are the usual early gastrointestinal symptoms of digitalis intoxication.[1,2,3] Herrmann[4] and his associates found them respectively 21, 18, and 12 times, in 44 cases of digitalis poisoning, but diarrhea only 5 times. Leaman[5] considered diarrhea a rare manifestation of overdosage. Occasionally it may be the only evidence of excess digitalis. Fishberg[6] mentioned a patient in whom the connection of diarrhea with the administration of digitalis was not recognized because of the absence of other symptoms. In his patient, as in the present patient, the diarrhea cleared up when the drug was discontinued.

Flutter, generally, is a relatively uncommon auricular arrhythmia, occurring approximately once to every ten instances of fibrillation.[2] The incidence of auricular flutter as a toxic effect of digitalis is even more rare. Some authors[1,2,3] have not mentioned it at all. Others[7,8] merely included it with the heterogeneous group of arrhythmias which can result from digitalis poisoning. Herrmann[4] and his associates, however, found only one instance of auricular flutter and ten instances of auricular fibrillation in a study of 44 patients having digitalis intoxication. Although the number of their patients is small, it is interesting to note that the frequency of flutter with respect to fibrillation as a toxic effect of digitalis parallelled the general relative incidence of these arrhythmias.

Since these authors[4] did not mention the amount or duration of digitalis therapy, it could not be determined whether they were dealing with initial or cumulative effects. McMillan and Bellet[9] described two patients with auricular flutter caused by acute digitalis intoxication and quoted Wedd[10] as being the first to describe the arrhythmia as a toxic effect of a single overdose of the drug.

In the subject under discussion, however, flutter and diarrhea were cumulative effects of maintenance doses of digitalis taken over a long period. The patient apparently had taken three grains of the powdered leaf daily for five years without ill effect until the onset of the presenting diarrhea. There was no evidence to point to increased absorption or decreased elimination of the drug to account for sudden toxicity. When digitalis was stopped the diarrhea ceased within 48 hours. Serial electrocardiograms showed decreasing digitalis effect, from flutter with the typical S-T segment and T wave digitalis contour, through auriculoventricular block, to normal configuration and rhythm.

The patient obviously had not been impressed with the fact that he was taking a powerful, potentially dangerous medication. He would not be aware of changes in the strength of the preparations he was using. The clinical effect[11] of digitalis standardized according to the United States Pharmacopeia XII (1942) was approximately 25 per cent weaker than U. S. P. XI which in turn was approximately 50 per cent stronger than U. S. P. X. If he had been conscious of the hazards, it is not likely that he would have continued it on his own for so long a time. This emphasizes the fact that a patient on digitalis therapy should be fully informed of its possible toxic manifestations. In addition, he should be made well aware of the necessity for proper medical supervision, not only during the initial phases of therapy, but as long as he is taking the drug. This aspect[12] is even more important if digitoxin or other of the purified glycosides are used, for then the toxic manifestations, being less prominent, will be less easily noticed.

SUMMARY

Auricular flutter and diarrhea are presented as unusual effects of chronic digitalis intoxication.

It is shown that with the discontinuance of the medication, the diarrhea ceased, the flutter stopped, and an evolution of decreasing digitalis effect was recorded in serial electrocardiograms.

The importance of properly informing the patient taking digitalis of its possible toxic effects is stressed.

The need for continuous medical supervision of the digitalized patient is emphasized.

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HEMOCHROMATOSIS WITH AURICULAR FIBRILLATION

A Case Report

Lieutenant (J.G.) W. R. Griffin (M.C. U.S.N.R.), Lieutenant (J.G.) H. G. Nelson (M.C. U.S.N.R.),* and Lieutenant-Commander J. R. Seal (M.C. U.S.N.)†

THE occurrence of clinical disorders of the heart in association with hemochromatosis has been rarely reported despite the fact that pathological studies have frequently described deposition of hemosiderin in the myocardium. Duncan[1] fails to mention either heart failure or arrhythmias as a part of the clinical picture or as a cause of death in his otherwise excellent description of the disease. Petit[2] in 1945, reported a case complicated by complete heart block. In a review of the literature, he located twenty-five case reports in which heart disease complicated hemochromatosis, out of which only four "adequate" reports were found in the English or American literature. All but three of the twenty-five patients were less than 45 years of age. Auricular fibrillation was described in two, auricular tachycardia in one, and complete heart block in two. Heart failure was the outstanding manifestation in the balance. Horns[3] has since added a case of heart failure attributed mainly to hemosiderin deposits in the myocardium.

CASE REPORT

R. A. W., a 49-year-old male veteran of American Indian-white extraction, was admitted on March 3, 1947, complaining of dyspnea, orthopnea, nocturia, and non-productive cough of about one year's duration. Three weeks prior to admission these symptoms had become more severe and swelling of the feet and ankles first appeared.

Upon physical examination the skin was described as "dark" and the mucous membranes and nail beds as "cyanotic." The neck veins were distended and pulsating, moist râles were present at the lung bases, the liver was enlarged and slightly tender, ascites was present, and there was moderate edema of the feet and legs. The heart was enlarged, the rate rapid, and the rhythm totally irregular. No murmurs were heard. The brachial blood pressure was 160/110 mm. Hg and the radial pulse 180 per minute.

Laboratory studies revealed an erythrocyte count of 3,250,000, but other findings, including the results of urinalyses, blood urea, and blood non-protein nitrogen were normal. The blood Kahn was negative. A roentgenogram of the chest showed cardiomegaly and severe pulmonary congestion. Serial electrocardiograms showed auricular fibrillation and a stable pattern of abnormal T waves. The venous pressure in the arm was 206 mm. of water and the arm-to-tongue circulation time, using Decholin, 44 seconds.

He was digatalized and kept at rest with prompt improvement. By the seventeenth day the arm-to-tongue circulation time had decreased to 16 seconds and the blood pressure had fallen to 134/82 mm. Hg. On April 7, 1947, he was discharged from the hospital on a maintenance dosage of 0.2 mg. of digitoxin daily.

The opinions stated herein are the private ones of the authors and are not to be construed as reflecting the opinions and policies of the Navy Department or of the Naval Service at large.

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On June 11, 1947, he was again seen as an outpatient and complained only of weakness and cramping of the legs. The blood pressure was 174/94-80 mm. Hg. Auricular fibrillation was again noted, the apical rate being 116 and the radial pulse rate 76 per minute. Evidences of congestive heart failure were present. It was again recorded that the skin has a "cyanotic appearance", said by the patient to have been "unchanged as long as he could recall."

On Dec. 31, 1947, he was admitted for the second time in a drowsy and confused state, complaining of cramping, numbness, and tingling of the legs. The family stated that moderate exertional dyspnea and periodic swelling of the feet and ankles had persisted and that moderate anorexia had developed within the past two months. They also stated that the skin had grown darker. Examination showed the skin to be a dark, slate-gray color (Fig. 1), and the mucous membranes were dry but free of pigment. The odor of acetone was present on the breath. The heart was enlarged, the rhythm totally irregular, the apical rate was 145 per minute and there was a pulse deficit of 70. Orthopnea, ascites, and edema were absent.

Fig. 1.—Photograph of patient on right showing deep coloration of the skin when contrasted to white boy of normal brunette coloring on left.

The urine had a specific gravity of 1.034, and gave a strongly positive test for sugar and a weakly positive test for acetone. The blood sugar was 500 mg. per 100 c.c. but other chemical analyses including the carbondioxide combining power, blood urea, blood chlorides, serum proteins, and albumin-globulin ratio were normal. The cephalin flocculation test was strongly positive within 24 hours and the icterus index was 14. X-ray film of the chest showed only a greatly enlarged cardiac silhouette. Electrocardiograms showed no specific changes from previous records and auricular fibrillation was still present. A biopsy of the skin from the abdominal wall was reported as showing an increased deposition of iron pigment compatible with a diagnosis of hemochromatosis.

The diabetes at first responded to regular insulin but later became increasingly difficult to regulate and the blood sugar levels ranged from 50 to 428 mg. per 100 c.c. During the fourth week of hospitalization he began to complain of nausea and pain in the right upper quadrant of the abdomen. An electrocardiogram showed no changes from previous records except for a ventricular rate of 190 per minute. On January 27, he began to vomit and became much weaker and more confused. On January 29, the blood sugar was 600 mg. per 100 c.c. On this date he lapsed into coma, exhibited signs of acute circulatory failure, and died. Final clinical diagnoses were hemochromatosis with diabetes, cardiac hypertrophy, auricular fibrillation, and congestive neart failure.

Autopsy was performed twelve hours after death at which time the slate-gray coloration of the entire skin was evident, being most prominent over the face, neck, arms, hands, and lower legs. There was also a slight pitting edema of the legs. Upon opening the abdomen, 500 c.c.

of clear, straw-colored fluid was found and the liver extended 5 cm. below the right costal margin. The pericardial sac contained 50 c.c. of a yellow, cloudy fluid and numerous small hemorrhagic areas were scattered throughout the serous surface of the pericardium.

The heart weighted 667 grams and was dilated and flabby. The cut surface of the myocardium was dark brown in color but showed no other gross abnormality. The aorta was normal except for a few scattered atheromatous plaques. The primary divisions of the coronary arteries also contained a few atheromatous plaques but the arteries as dissected out were widely patent and showed no evidence of obstruction.

Upon section the lungs were grayish-brown in color and exuded frothy fluid upon the cut surface of both lower lobes. The liver weighed 3,290 grams. It was firm, dark brown in color, and finely nodular. The spleen weighed 623 grams, was firm and fibrous, and the capsule showed a fibrous thickening measuring 1 to 3 mm. The pancreas, adrenal medulla, and anterior lobe of the pituitary also showed brownish pigmentation. The visceral lymph nodes varied from brown to black. The kidneys were grossly normal except for congestion and indistinct demarcation of the cortex from the medulla.

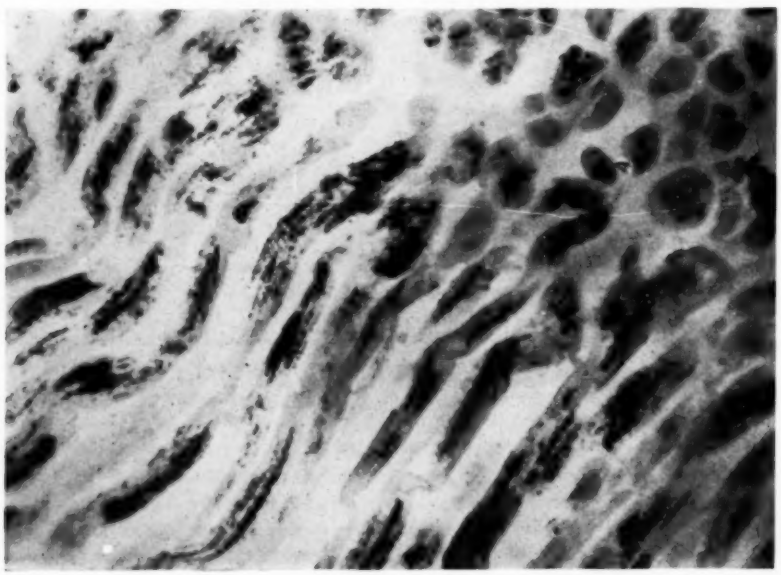

Fig. 2.—Photomicrograph of myocardium from left ventricle showing extensive hemosiderin deposition in myocardial fibers.

Sections* of the heart showed a fibrous thickening of the epicardium which was infiltrated with moderate numbers of lymphocytes, plasma cells, and a few neutrophiles. The fibers of the myocardium were large and contained a large amount of iron pigment, often situated in a bipolar arrangement (Fig. 2). The nuclei in some areas were quite large and pale. There was a considerable increase in interstitial fibrous tissue in which was seen many histocytes containing iron pigment. There were no recognized abnormalities of the endocardium, aorta, or coronary arteries.

Sections of the lungs and liver showed the usual findings of chronic passive congestion, cells containing hemosiderin being found only in the alveoli of the lungs. There was a marked

*Histological studies were made on sections stained with both hematoxylin and eosin and with special stains for iron pigment. The latter sections were prepared, and all sections reviewed, by Lieutenant (J.G.) J. R. Carter (M.C. U.S.N.), Pathologist at the Naval Medical School, Bethesda, Md.

increase in the fibrous tissue of the portal areas of the liver with hyperplasia of the small biliary ducts in these areas. Large amounts of iron pigment were present in the parenchymal cells, the Kupfer cells, and in many of the cells scattered through the fibrotic portal areas. In the spleen, iron-containing histocytes were found most frequently adjacent to the trabeculae and blood vessels and there were large fibrous nodules throughout the parenchyma which contained deposits of iron pigment. The pancreas showed a considerable interstitial fibrosis in which there was a large amount of iron pigment. There were also moderate amounts of iron pigment in the epithelial cells of the gland. The islets were small and surrounded by an increased amount of interstitial tissue containing large numbers of iron-pigmented histocytes. The cells of the islets also contained small amounts of iron pigment. A varying amount of iron pigment was also found in the adrenal medulla, convoluted tubules of the kidney, lymph nodes, and skin. In the anterior lobe of the pituitary there was a selective deposition of iron in the chromophobe cells although minute amounts were also seen in the basophile and eosinophile cells. The kidneys were essentially normal except for congestion. The smaller arteries throughout the various sections were essentially normal except for an occasional deposit of iron pigment in their media or adventitia. The arterioles showed none of the changes usually associated with a primary vascular disease or sustained hypertension. Final anatomical diagnosis were: hemochromatosis, fibrosis and hypertrophy of the heart, pulmonary congestion and edema, and chronic passive congestion of the liver.

COMMENT

The original clinical findings in this patient, ten months prior to his death, were those of cardiac enlargement, auricular fibrillation, elevation of blood pressure, and congestive heart failure. The unusual skin color, noted at that time, was ignored probably because of the lack of a history of color change, the racial extraction of the patient, and the absence of sugar in repeated urinalyses. In retrospect, a skin biopsy or the skin test suggested by Fishback[4] would probably have led to a diagnosis of hemochromatosis at that time had the pigmentation aroused suspicion.

It was of interest to note the rapid progression of the disease and the late development of the diabetes. The exact duration of the diabetes is unknown, as the confused state of the patient during his final admission precluded an accurate history. Available information would indicate that it developed within the two months prior to his terminal illness and Duncan[1] states that death usually occurs within twelve months after diabetes is first detected.

French writers, reporting most of the cases of cardiac disorders in association with hemochromatosis, are convinced that such disorders are due directly to the deposition of iron pigment. In this case, no other explanation could be found to explain the arrhythmia and heart failure. An elevated blood pressure was found only during the more severe stages of congestive heart failure and the usual pathological changes of a sustained or progressive hypertension were absent at post-morten examination. There was no evidence of any significant degree of atherosclerosis of the coronary arteries on either gross examination or in the sections. On the other hand, extensive fibrosis was seen in all areas where there was a heavy deposition of iron pigment, this being most prominent in the heart, liver, and pancreas. There seems to be every reason to believe that the extensive iron deposits in the myocardium were responsible for the clinical and anatomical evidences of damage to that organ and that the auricular fibrilla-

tion, a rarely described manifestation of the heart disease associated with hemochromatosis, was probably the precipitating factor for the heart failure in this patient.

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AUSCULTATORY EVIDENCE OF CARDIAC RUPTURE

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THE circumstance of a physician hearing a rupture of a heart wall is fortuitous and rare. A search of the Index-Catalogue of the Library of the Surgeon General's Office and their Subject Index revealed only one reference to such an event. That was a report by Reznikoff.[1] The sounds were described as follows:

> "During these two minutes a stethoscope was clapped to his chest, and over the precordium was heard an extraordinary sound. A continuous, muffled, low-pitched rushing rumble, louder during the expiratory phase, dimmed during the few inspiratory periods, was constantly heard. No heart sounds were evident. All this transpired so quickly that only two auditors could listen to this remarkable murmur. Its significance was not apparent, and at first it was imagined by the observers that the sounds were such as might be heard over a fibrillating ventricle."

A necropsy revealed:

> "Irregular laceration of the wall of the left ventricle in immediate proximity to the interventricular septum situated midway between the base and apex of the heart. This laceration was 3 cm. in length and ran obliquely downward and to the right directly over the course of the corresponding coronary artery."

The following paragraphs describe an instance in which the precordium was under auscultation for a short period before the rupture occurred, during the time of rupture, and until the patient expired. The sounds observed in this instance were quite different than those noted by Reznikoff.

CASE REPORT

An 84-year-old white woman who had been a private patient over a period of eight years was seized on the morning of Feb. 5, 1949, with severe midsubsternal pain radiating down both arms to the wrists. The pain was of several hours' duration, requiring two hypodermics of Demerol for relief. There was profuse perspiration and vomiting. The patient was pale; the blood pressure was 110/80 mm. Hg; the pulse rate was 72 and regular; the heart sounds were distant. She was admitted to the hospital and there, at 4 P.M., a third injection of 100 mg. of Demerol was given to relieve her pain. On the following morning she was still complaining of some left chest pain, accentuated on deep breathing. The blood pressure was 115/80 mm. Hg and a soft friction rub was heard over the left precordium. Her temperature was 100° F. on the second day of admission; 99.6° F. on the third; and not above normal on the fourth or fifth, the latter being the day of her death.

Her only previous illness of note was malaria in 1884. A total hysterectomy was done for uterine fibroids in 1908. She was known to have had hypertension since 1941. Her blood pressure varied from 210/90 mm. Hg to 230/90 mm. Hg; in the latter years her pressure was averaging 180/90 mm. Hg. There was a moderate hypertrophy of the left ventricle by x-ray, and an occasional electrocardiogram was interpreted as normal.

On admission to hospital the patient was alert and cooperative. The pulse was 96 and regular, the blood pressure 115/80 mm. Hg; a friction rub was heard in the fourth interspace 6 cm. to the left of the sternum (this friction rub disappeared in the following twenty-four hours). No murmurs were heard. Moist râles were present over the left base posteriorly. There was some edema of each ankle. Laboratory procedures soon after admission showed a white blood count of 13,450, 89 of which were segmented polymorphonuclear leucocytes, 8 lymphocytes, and 3 monocytes; the red cell count was 3,880,000 per c. mm.; the hemoglobin was 12 Gm., or 78 per cent; sedimentation rate was 19 mm. in one hour (Westergren method). The prothrombin time was 20 seconds (control 18 seconds), prothrombin concentration 28 per cent. The electrocardiogram on admission presented a normal sinus rhythm of 85. The P-R interval was 0.20 second, QRS interval 0.08, R-T interval 0.30. Graphic interpretation: QRS complexes had a tendency to low amplitude in limb leads and in aV_L aV_F. The Q wave in $V_{2,4}$ was wide and deep; $S\text{-}TV_{2,4,5}$ elevated; interpretation: anterior infarction. In a second electrocardiogram seventy-two hours later, the T_2 was lower, $S\text{-}T_{2,3}$ elevated, Q_3 deep, T_3 inverted, $S\text{-}TaV_F$ depressed, $S\text{-}TV_2$ elevated, coving $S\text{-}TV_{2,4,5}$. Electrocardiographic impression: definite change since previous electrocardiogram, suggesting spread of infarct to the posterior wall.

On the morning of February 9 (fourth day of her acute illness), the patient was comfortable, the blood pressure was 120/80 mm. Hg, the heart sounds were slightly distant, no friction rub was heard, and the rhythm was regular. The lung fields were free of râles, the liver was not enlarged, there was no calf tenderness. I visited with her for a few minutes, again placed my stethoscope over the apex and heard several cycles of normal sound. While listening, there suddenly occurred a loud, harsh murmur that filled the entire systolic period. The murmur began abruptly and ended abruptly. It was followed by four further murmurs of like description but of diminishing intensity. The murmur then disappeared entirely and the following four cycles of the heart were muffled and poorly defined. There was no detectable change in rhythm. The patient then had a convulsion and expired.

The post-mortem examination was performed by Dr. Paul Riparetti one-half hour after death. The tissues were reviewed by Dr. George J. Hummer. The pertinent findings of this autopsy study were:

"The pericardial sac is distended and has a bluish color. On opening, an estimated 250 c.c. of fresh and clotted blood is expressed. There is a recent pericarditis, evidenced by stringy material attached to the epicardium, located chiefly over a defect, to be described.

"The heart weighs 290 grams. There is a rupture of the left ventricle on the anterior surface, measuring 20 mm. in length; the defect is linear and a probe can be passed into the chamber of the left ventricle. Surrounding this area the epicardium is discolored, reddish, and for a distance of 3 or 4 cm. the epicardium is the site of a recent shaggy pericarditis. The entire apex of the heart has a black discoloration and is softer than other regions. The chambers are opened in the usual manner. The auricles are normal and no congenital abnormality is found. The ventricles will be described in detail." (The description of the heart valves is not pertinent and therefore is omitted.)

"The left ventricle is 22 mm. thick, the right ventricle 5 mm. In the region of the interventricular septum there is an aneurysmal dilatation of the wall 7 cm. in diameter; this has encroached on the interventricular septum so that this area is very thin, only 2 mm. in thickness. The area of the linear defect is extremely thin, only a few millimeters as compared with the normal wall.

"The coronary arteries show advanced arteriosclerosis. There is complete occlusion of the anterior descending branch of the left coronary artery about 15 mm. beyond its ostium; this defect

measures several millimeters in length. The myocardium supplied by this artery is yellowish and brownish red and occupies the apex of the heart, mostly on the left ventricular side but also running over to the right ventricle and along the interventricular septum; this defect measures several centimeters in diameter and the myocardial infarct in this area is estimated to be at least older than 5 days."

The anatomical diagnoses were in part as follows:

Arteriosclerosis of the coronary arteries, advanced.

Recent occlusion of the anterior descending branch of the left coronary artery.

Recent infarct in the anterior wall of the left ventricle.

Aneurysmal dilatation of the anterior wall of the left ventricle with rupture.

Hemopericardium (250 c.c. of blood).

Recent pericarditis.

SUMMARY

An instance of rupture of the anterior wall of the left ventricle is described, during which time the entire cycle of changes from normal heart sounds through the period of rupture and until cessation of heart action, is recorded. A diagnosis of ruptured ventricular wall was entered on the hospital record at that time; it was substantiated by post-mortem examination.

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PRIMARY ANGIOSARCOMA OF THE HEART

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THE rarity of primary angiosarcoma of the heart is indicated in the recent review by Whorton[1] who states that only four such tumors have been previously reported.

The variety of clinical manifestations of tumor of the heart prevents the delineation of a specific syndrome. Yater[2] has listed certain features of symptomatology suggestive of tumor of the heart. These include heart block without readily apparent cause; other symptoms referable to the location of the tumor such as unusual distribution of edema, attacks of intense dyspnea or cyanosis with change of position, or signs of tricuspid and pulmonic stenosis; symptoms of cardiac dysfunction without apparent cause in a patient with a known malignant process; accumulations of hemorrhagic pericardial and pleural fluid; and certain suggestive roentgen observations. Although cardiac embarrassment by tumor may be minimal despite massive involvement of the heart, intractable heart failure without obvious cause should attract attention to the possibility of neoplasm of the heart.[1] In Shelburne's case,[3] rheumatic fever was suspected because of the presence of the major manifestations of this disease, carditis and arthralgia, and of the minor manifestations, fever, precordial pain, leucocytosis, and increased sedimentation rate. Simulation of bacterial endocarditis may occur when emboli arise from the cavities of the heart.[2] The occurrence of emboli characterized the case of hemangioendothelioma of the heart reported by Gross and Englehart.[4]

McCandles and Faloon[5] have reviewed the use of cytological examination of pericardial fluid in the diagnosis of tumor. They found only ten cases reported in the American literature, prior to their own, in which malignant cells were demonstrable in the pericardial fluid.

CASE REPORT

A. G., a 45-year-old Negro woman, was admitted to the John Gaston Hospital because of malaise, weakness, lethargy, anorexia, ill-defined anterior chest pain, pain in the abdomen, and weight loss. Following the delivery seven months previously of a normal infant, the patient had been in good health until two months before admission when swelling of the face was first noted. Progressive lethargy ensued a month later. Vomiting began to occur about twice daily; the vomitus consisted of clear water. Bowel movements during the past three weeks had been associated with right lower quadrant abdominal pain, and feces were occasionally watery. Shortness of breath and nocturnal dyspnea were denied.

From the Departments of Medicine and Pathology, University of Tennessee, College of Medicine, and the John Gaston Hospital, Memphis, Tenn.

Physical examination disclosed temperature of 95.2° F., pulse 100, respiratory rate 28, and blood pressure 90/70 mm. Hg without pulsus paradoxus. The patient appeared apathetic, weak, chronically and seriously ill. Neck veins were engorged and the eyelids and forehead were slightly edematous. The breath sounds were bronchial in character over the apex of the left lower lobe. The cardiac apical impulse was in the fifth left intercostal space in the midclavicular line. The cardiac dullness extended beyond the apical impulse to the anterior axillary line and well to the left of the sternum in the second and third intercostal spaces. The heart sounds were of fair quality and regular with no adventitious sounds. The liver was enlarged, smooth, and tender, extending four fingerbreadths below the right costal margin in the midclavicular line. Moderate gaseous distension of the lower abdomen was present. The skin was dry and cool, and slight bilateral ankle edema was observed. Pelvic examination revealed a foul, pink, vaginal discharge. A cyst in the left labium majorum was present.

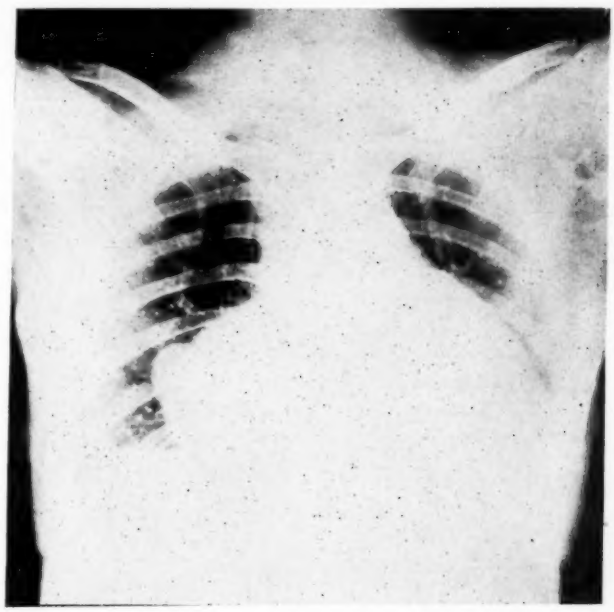

Fig. 1.—X-ray examination of the chest demonstrates the water-bottle contour of the cardiac silhouette and the nodular protuberance on the right margin.

Hemoglobin was 11 Gm. per 100 c.c. of blood, red blood cell count 3.2 million per c. mm. and white blood cell count 15,950 per c.mm. The urine showed specific gravity of 1.022, 1-plus albumin, and a few leucocytes and hyaline casts in the high power microscopic field. The blood nonprotein nitrogen was 136 mg. per 100 c.c. The blood chlorides were 390 mg. and carbon dioxide combining power 37 volumes per 100 c.c. Total serum protein was 6.6 Gm. with 3.9 Gm. albumin, 2.7 Gm. globulin. Serum bilirubin was 1.3 mg. direct, 2.4 mg. total.

X-ray examination of the chest (Fig. 1) revealed marked enlargement of the cardiac silhouette. The contour was water-bottle in shape, but with a nodular protuberance on the right border. At fluoroscopy cardiac pulsations were absent. Several calcified lesions were seen throughout both lung fields. The findings were interpreted as representing pericardial effusion due to metastatic malignancy. The electrocardiogram (Fig. 2) showed a rate of 100, a P-R interval of 0.16 second, and a QRS of 0.08 second. The T waves in Leads II, III and aV_F were inverted; the T wave in Lead aV_R was upright.

Pericardial tap yielded 300 c.c. of bloody fluid with a specific gravity of 1.013 and total protein content of 4.3 Gm. per 100 c.c. The fluid contained 2,150 leucocytes per c.mm., the majority of which were lymphocytes, and had a hematocrit of 1 per cent. Papanicolaou stain revealed tumor cells (Fig. 4,*B* and *C*).

The patient failed to improve after pericardial centesis. The blood pressure remained at shock levels. The skin continued to be cold, distension of neck veins and hepatomegaly persisted, and the patient expired twenty-four hours after admission.

Autopsy revealed an angiosarcoma of the right atrium with metastases to the right ventricle and the lungs, hemopericardium, and severe chronic passive congestion of the abdominal viscera.

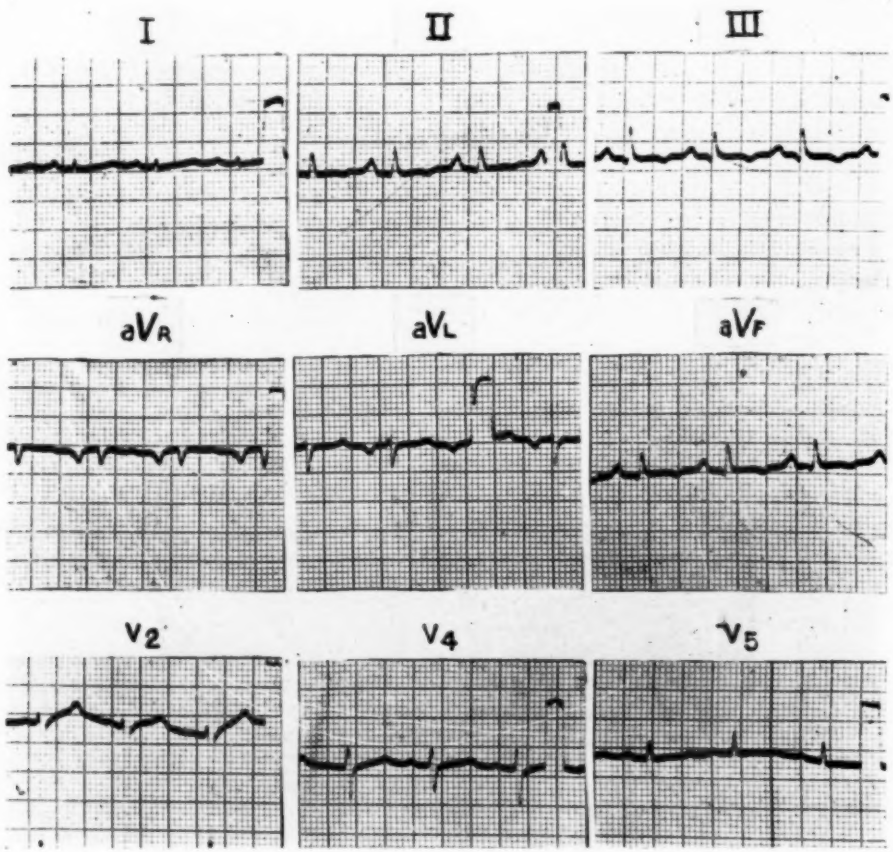

Fig. 2.—Electrocardiogram shows low voltage and evidence of myocardial abnormality.

The well-developed, poorly nourished body of a 45-year-old Negro woman showed mild pedal edema, but no ascites or hydrothorax. The pericardial sac, partially obliterated by fibrous adhesions, contained 300 c.c. of clotted and fluid blood. Approximately half of the cardiac weight of 640 grams was due to a large (8 × 5 × 5 cm.), globular, dark-red mass arising from the interatrial septum and projecting into the right atrium and partially through the undilated tricuspid orifice. The right atrium was almost completely filled and the tricuspid valve area obstructed (Fig. 3). The free surface of the projecting tumor was smooth. There were several small, reddish tumors over the rest of the right atrial and right ventricular endocardial surface, but none were

Fig. 3.—The large polypoid angiosarcoma is seen arising from the right auricular wall and projecting through the tricuspid orifice. The right side of the heart has been opened posteriorly along the septum and the lateral wall reflected.

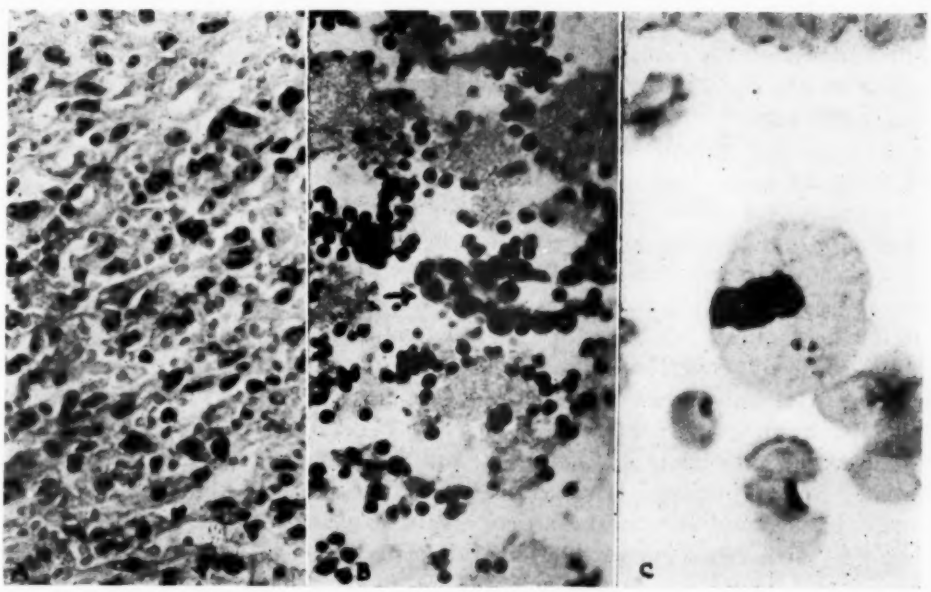

Fig. 4.—*A*, the tumor tissue is characterized by many fine vascular channels containing erythrocytes and lined by endothelial cells with large, hyperchromatic nuclei.

B, this group of exfoliated cells in the pericardial fluid are considered as angiosarcoma cells, although they closely resemble mesothelium.

C, a large cell is seen in the pericardial fluid prepared by the Papanicolaou technique. The nearby erythrocytes indicate the relative size of the large cell which is thought to be from the angiosarcoma.

found in the unaltered tricuspid valve, the left ventricle, or left atrium (including the left aspect of the interatrial septum). Several separate tumor nodules projected from the right atrial myocardium into the pericardial sac. They were associated with some fibrous adhesions, and focal adhesions were scattered throughout the pericardial sac. All tumor nodules, when sectioned, had a dark-red hemorrhagic structure; the larger, intra-atrial mass had reddish zones of coarse, fasciculated bands and dark-red hemorrhagic areas.

Microscopic examination of the cardiac tumor revealed a fairly uniform pattern of closely grouped, small channels containing erythrocytes, lined by plump endothelial cells with vesicular nuclei, and peripherally outlined by delicate reticula and, occasionally, by collagen stroma (Fig. 4,*A*). The hemorrhagic areas differed from the paler zones only in the quantity of blood in the vascular channels. In the right ventricular myocardium there were many minute, separate tumor masses which were often in direct contact with the cardiac chamber. There was no endothelial covering or thrombus. Small groups of tumor cells were also present in thin-walled veins or dilated capillaries of the heart. There were focal hemorrhages in the epicardium and aggregates of lymphocytes and phagocytes containing ochre (iron-positive) pigment.

The right lung weighed 350 grams and the left 420 grams. Both had focal, fibrous, pleural adhesions, many calcified subpleural nodules measuring up to 2.5 cm. in size, increased consistency, and congestion of the bases with small scattered hemorrhages. On microscopic examination a few minute metastases were found in small pulmonary arteries, attached to portions of the walls, and extending into the lumina. The pulmonary metastases were not only histologically identical to the cardiac tumor, but were similarly unassociated with thrombosis or endothelial covering. There were no metastases to the tracheobronchial lymph nodes.

Other changes consisted of severe passive congestion of the gastrointestinal tract, liver, spleen, and kidneys, a Bartholin gland cyst, and endometrium in menstrual phase.

COMMENT

This case presented outstanding evidences of cardiac tumor: signs of right heart failure, bloody pericardial effusion, and irregularity of the right cardiac border on the roentgenogram. Right-sided cardiac failure resulted from mechanical obstruction to the blood flow by the polypoid, globular angiosarcoma of the right atrium. The tumor not only filled the right atrium but occluded the tricuspid orifice and partially obstructed the orifices of the venae cavae and coronary vein. Apparently, blood oozed directly into the pericardial sac from the angiosarcoma. The tumor was in direct contact with the intracardiac blood. Presumably this could be the source of metastases to the right ventricle and atrium. However, the Thebesian venous network is a plausible route of metastases since venous tumor emboli were found in the heart. This explanation has been offered by Yater[2] for the predominance of metastases to the right side of the heart while the left ventricle and atrium are spared. Approximately 60 per cent of the venous blood empties through the Thebesian veins into the right atrium and ventricle; only 20 per cent finds exit through the Thebesian veins into the left atrium and ventricle; and the remainder empties through the coronary veins.[6] Gregg,[7] however, believes that most of the right coronary arterial blood empties into the anterior cardiac veins and the coronary sinus while very little blood enters the right side of the heart by the Thebesian veins. Anastomotic channels are more numerous on the right than on the left side of the heart. Not only are there anastomoses between the subepicardial and deeper veins of the heart but also between these cardiac channels and the extracardiac veins draining into the superior and inferior venae cavae. Even though such

observations on animals can not be applied uncritically to man, they do emphasize the extensive anastomoses between the vessels of the heart. These anastomoses help explain the intracardiac metastases in this patient.

Primary malignant tumors of the heart are rare, only 100 having been reported according to Whorton.[1] Nevertheless, it appears that most primary cardiac tumors arise in the right side and especially the right atrium. In attempting to establish the histogenesis for primary cardiac tumors it has been hypothecated that all arise from a primitive or embryonal mesenchyme. When one considers that the last zone for complete structural formation is in the septal area, this concept seems a less remote possibility. As for angiosarcomas specifically, it is interesting to note that angiomas or varices of the endocardium are most common about the foramen ovale. Although Greenberg and Angrist[8] suggest that many reported cases of angioendotheliomas of the heart represent instances of vascularization of thrombi, the histologic features as well as the metastases of our patient confirm the occurrence of true malignant angiomas in the heart. One can not predict in this instance what significance pregnancy may have had upon the development or growth of the tumor.

SUMMARY

The clinical and pathological findings in a case of primary angiosarcoma of the right atrium are presented. Clinical manifestations were evidences of right heart failure, hemopericardium, and irregularity of the right cardiac border on roentgenogram.

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RHABDOMYOSARCOMA OF THE HEART

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THERE are approximately 200 recorded cases of primary tumor of the heart in the literature, of which 20 per cent are malignant.[1] Among the malignant tumors, rhabdomyosarcoma is one of the rarest. Apparently the first case was reported by Bradley and Maxwell in 1928.[2] In a limited review of the literature we are able to find only five other cases of rhabdomyosarcoma of the heart reported to date.[2-6]

Clinically there are several findings which tend to suggest the presence of a tumor of the heart. Among these are: an intractable myocardial insufficiency without a history of previous heart disease and without other demonstrable cause of heart disease; signs of mediastinal tumor, particularly when associated with changes in the appearance of the heart on roentgenological examination; heart block, other conduction disturbances, and arrhythmias; and recurrent hemorrhagic pericardial or pleural effusion.[3,7]

We are reporting this case of rhabdomyosarcoma because of its rarity, its interesting clinical findings, and because the diagnosis of tumor of the heart was suspected ante mortem.

CASE REPORT

J. R., a 43-year-old Negro man, was first seen on July 31, 1947, complaining of pain in the chest. He stated that the present illness began two years previously, at which time he noted a catching pain in the right chest. From the onset the pain had recurred occasionally, but had never been severe until July 28, 1947, when it recurred, lasting until admission with only brief periods of relief. There had been no cough, hemoptysis, or exertional dyspnea. His appetite had remained good. The history was otherwise negative.

He was well developed and well nourished with shallow respirations at a rate of 28 per minute. The pulse was 68 and the temperature was 100.4° F. The pharynx was slightly injected. Increased breath sounds were present at the right base posteriorly, without alteration in percussion or palpation. The blood pressure was 122 mm. Hg systolic and 80 mm. Hg diastolic. The heart was not enlarged by percussion and no murmurs were heard. The liver and spleen were not palpable and there was no edema.

The hemoglobin on admission was 11.5 Gm. or 74 per cent. There were 8,600 white cells with 63 per cent neutrophiles, 24 per cent lymphocytes, and 13 per cent monocytes. The urine was normal. Three sputum examinations were negative for acid-fast bacilli. Blood culture was negative on two occasions. Agglutinations for typhoid, paratyphoid, brucella, tularemia, and proteus bacilli showed low titer changes not of diagnostic importance. The sedimentation rate (Cutler) was 22 mm. per hour (normal 10).

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His fever rose until it reached 103.6° F. on the third hospital day, Aug. 2, 1947, and remained at about that level until Aug. 7, 1947. He was started on penicillin 30,000 units every three hours on Aug. 5, 1947, but an afternoon rise in temperature to 100 or 101° F. continued until his discharge, Sept. 2, 1947.

Fig. 1.—Erect posteroanterior view of chest showing right-sided enlargement of the heart.

On Aug. 6, 1947, x-ray of the chest, right lateral and anterior views (Fig. 1), showed what appeared to be an enlargement of the heart to the right. The lung fields were considered clear. On Aug. 7, 1947, fluoroscopy and films revealed enlargement of the cardiac silhouette, chiefly on the right in the region of the right auricle. Pulsations were noted in this region but were less than on the left side of the heart. The lung fields were clear bilaterally. The aorta appeared normal throughout its thoracic extent and there was no change in the cardiac silhouette with change of the patient's position to a 65 degree Trendelenburg position.

On August 7, the electrocardiogram (see Fig. 2) showed an apparent absence of P waves with nodal rhythm.

On August 14, the circulation time from the left antecubital vein showed the arm to tongue time (using Decholin) to be 30 seconds, arm to lung time (using ether) 16 seconds. This procedure was repeated on Aug. 16, 1947, the arm to tongue time was 27 seconds and the arm to lung time was 12 seconds. The venous pressure was 110 mm. water. He continued to complain of pain in the right chest until August 25, at which time it subsided and he left the hospital on Sept. 2, 1947.

On April 8, 1948, he returned complaining of exertional dyspnea, pain in the chest, and hemoptysis. He was advised to enter the hospital but failed to do so.

He returned for admission on June 2, 1948, complaining of hemoptysis of six weeks' duration. For the past six weeks he had had a persistent cough productive of phlegm, more in the morning. The chest pain had grown steadily worse in the past six weeks and hemoptysis occurred occasionally. He had noted fever, anorexia, weakness, and considerable weight loss for the past two months. His feet and legs became edematous when in a dependent position.

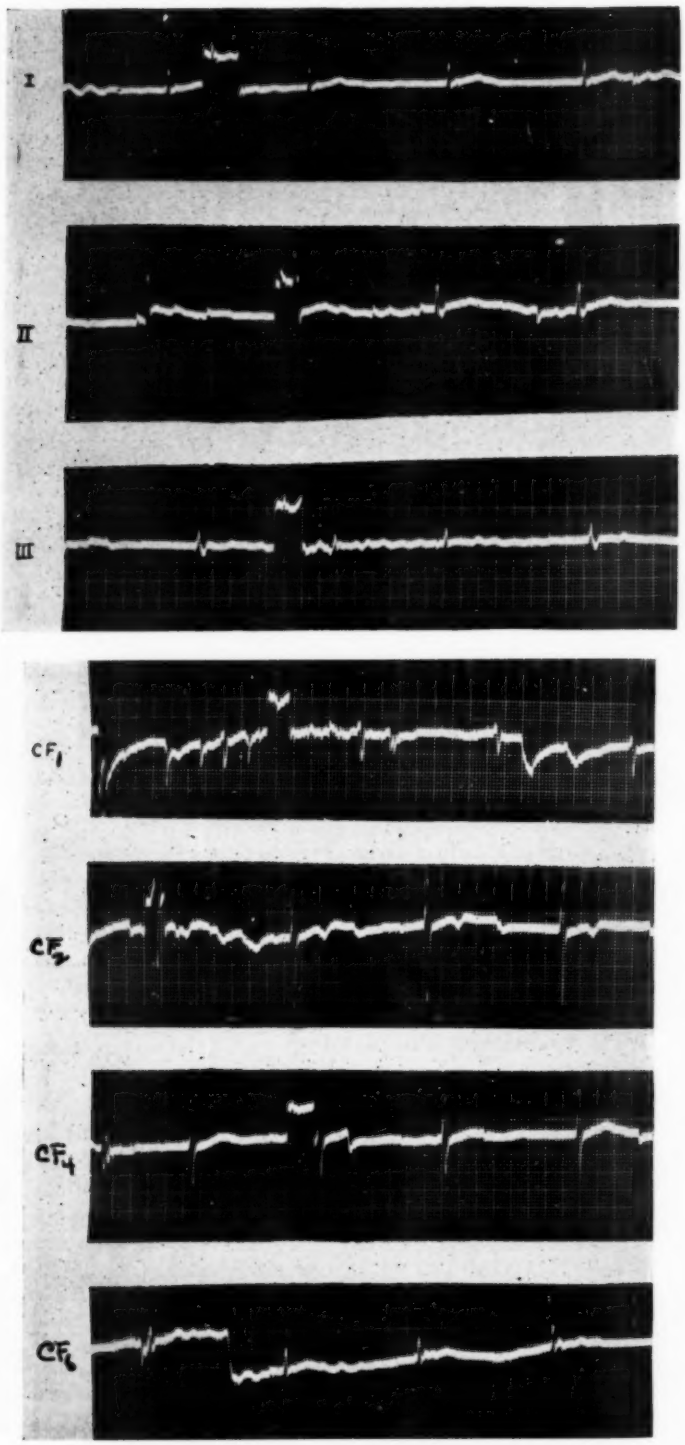

Fig. 2.—Electrocardiogram showing absent P wave with nodal rhythm.

Examination on admission showed an undernourished Negro man, dyspneic with a persistent cough, expectorating a blood-tinged sputum. Flatness to percussion and absence of fremitus and breath sounds were present posteriorly and laterally over the left chest. Fine crackling râles were present over the right base anteriorly and posteriorly. The blood pressure was 126 mm. Hg systolic and 78 mm. Hg diastolic; the rhythm was regular and no murmurs were heard. No enlargement of the heart was detected. A one plus pedal edema was present. The afternoon temperature was 101° F.

On admission, the hemoglobin was 45 per cent, or 7 Gm. The urinalysis was negative and sputum examinations were negative for acid-fast bacilli on six different occasions. Thoracentesis of the left chest was performed on June 7 and 14, 1948, with the removal of 1,100 c.c. and 1,750 c.c. of bloody fluid which, on microscopic examination (Dr. W. R. Mathews) showed malignant cells.

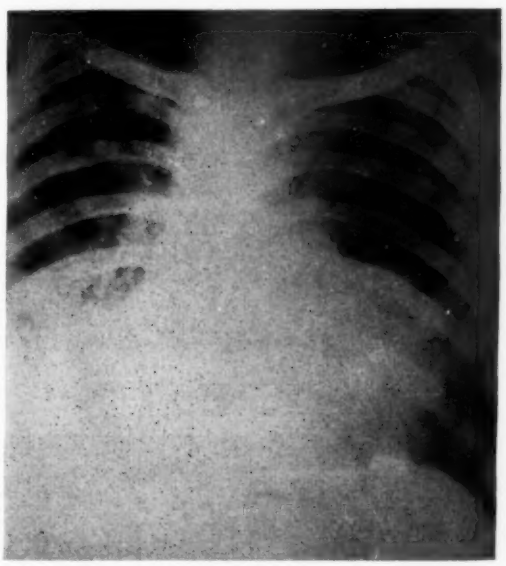

Fig. 3.—Erect posteroanterior view of chest showing consolidation in both bases and rounded areas of consolidation in both lungs.

On June 4, 1948, an erect posteroanterior view of the chest (Fig. 3) showed extensive consolidation in both bases, and throughout both lung fields there were seen faint yet definitely perceptible rounded areas of consolidation.

He became rapidly worse and expired on June 16, 1948.

Post-mortem examination showed a well-developed Negro man, 43 years old. The extremities were equal, there was a 2 plus pitting edema of both feet and legs. No jaundice or palpably enlarged nodes were present.

The right pleural cavity contained 600 c.c. of bloody fluid and the left 1,200 c.c. The visceral pleura of both sides was thickened and adherent in portions to the parietal pleura. The adhesions were due to metastatic disease involving the pleura.

The left lung was collapsed and weighed 1,000 grams. The pleural surface was covered with firm, raised, nodular masses measuring as much as 4 cm. in diameter. Cut section of the lung revealed these nodules to be throughout the lung parenchyma. The right lung was markedly adherent to the pericardial sac by a dense growth of tumor. The right lung was covered by nodules similar to those of the left lung. Deep-seated nodular masses as large as 4 cm. were found in the parenchyma on cut section of the lung.

The pericardial sac was thickened and adherent to the right lung and diaphragm. The pericardial cavity was completely obliterated by metastatic disease. The heart was a huge, rather triangular mass which measured 25 by 18 by 15 centimeters. There was a huge tumor mass which infiltrated the right auricle posteriorly (Fig. 4) and the posterior portion of the right ventricle and tricupsid valve (Fig. 5). Section of the tumor revealed a cut surface of brownish-red color, hemorrhagic and friable in character. The left ventricle was free of tumor grossly, the wall measuring 0.8 cm. in thickness. The right ventricular wall anteriorly measured 1.0 cm. in thickness in an area where no tumor was grossly present.

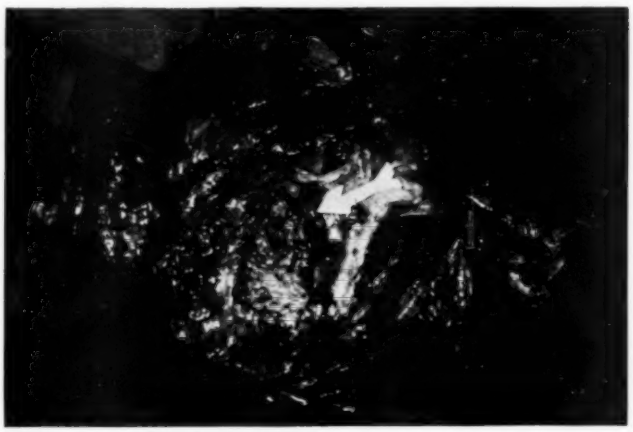

Fig. 4.—Tumor mass in right auricle.

Fig. 5.—Tumor mass on tricuspid valve and in right ventricle.

The left upper lobe bronchus showed on its posterior surface about 3 cm. from the bifurcation a hemorrhagic reddish-brown, friable mass that measured 3 by 2 centimeters.

The liver, spleen, kidneys, and intestines showed only congestion.

Microscopic study by the pathologist (Dr. W. R. Mathews) was reported as follows: "Sections (Figs. 6 and 7) from different parts of the tumor in the heart wall and metastatic lesions of lungs showed variable structure, largely depending on the presence or absence of necrosis and hemor-

rhage. Broad areas of hemorrhagic necrosis with widely separated small foci of tumor, usually surrounding blood vessels, form the outstanding finding of some of the sections. In other sections ovoid or elliptical-shaped areas of nonhemorrhagic necrosis scattered at random through the tumor are noted. In sections showing well-preserved tumor, the cell bundles are fasciculated in places, while in other areas they occur in broad sheets without pattern or design. The tumor cells mainly fall into two types: fusiform or straplike and giant cells. The cytoplasm is acidophilic and shows longitudinal and occasionally rather indistinct cross striations. Eosinophilic ribbonlike bands and areas of deeply eosinophilic granular or homogenous material which may or

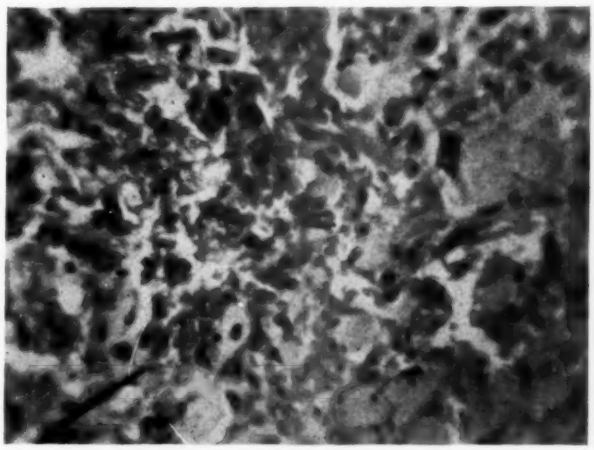

Fig. 6.—High-power view of section of tumor.

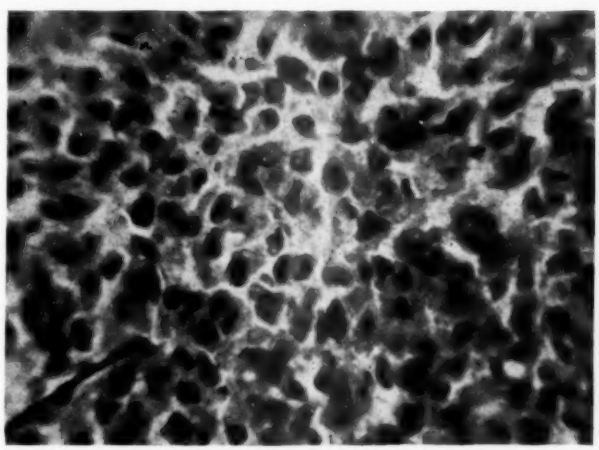

Fig. 7.—High-power view of section of tumor.

may not contain pyknotic nuclei are present. The nuclei are usually voluminous and show prominent nucleoli and a moderate number of mitoses. The giant cells vary in size, usually contain multilobed nuclei, and show bizarre features belonging to muscle cells.

Diagnosis: Rhabdomyosarcoma."

COMMENT

This case presented four clinical findings suggestive of primary tumor of the heart, intractable myocardial insufficiency in the last few months of life, otherwise not explained, depression of S-A node with nodal rhythm, roentgenographic evidence of enlargement of the heart of an unusual pattern, and finally recurrent hemorrhagic pleural effusion.

The site of origin was thought to be in the right auricle with extension to the tricuspid valve and right ventricle, and metastasis to the pleura, lungs, and pericardium.

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Editorial

MERCURIAL DIURETICS

ELSEWHERE in this issue there is found a personal account of the discovery of the diuretic action of certain mercurial compounds. The facts which led to this have not previously been published, so it seems particularly opportune that they should be presented on the thirtieth anniversary of the discovery. The history of Medicine would be more illuminated and enlivened if more of the simple beginnings were recorded.

It would seem fair to state that this was the greatest advance in the treatment of chronic congestive heart failure since Withering published his classical account of digitalis in 1785. Whereas Withering received his tip, so to speak, from an empirical herbalist, it required shrewd observation and patient exclusion by trial and error to determine eventually the potent ingredient from a conglomerate mixture of herbs and roots which were the customary therapeutic preparations of his time. It might be held that his information came to him by chance, but others must have heard of the herbalist's secret and did nothing about it. So may have been the case with the diuretic action of mercury.

In the early years of the last century, a favorite preparation of digitalis was a pill combining one grain each of digitalis and squills. Squires' Companion to the British Pharmacopoeia of 1871 lists a pill containing digitalis, squills, and blue mass. The amounts of each were found to vary in the formularies of the different hospitals—from one-half grain to one grain of digitalis and one to three grains of blue mass. The amount of squills also differed somewhat, but was usually one grain. This pill became known as Guy's, Bailley's, or Niemeyer's pill, and it commonly contained one grain of each substance. The value of the digitalis and squills is easily understood, but why the mercury? It is not likely that it was for its purgative effect but probably rather because its combination with the other two was found to enhance their diuretic action. It must be further appreciated that a century ago pharmacology as we know it today did not exist. Drug therapy was entirely empirical and renal physiology practically unknown.

Johanna _____ could not have been an unusual case in herself. As Dr. Vogl points out, the unusual feature of this unconscious experiment was the careful and accurate record kept by the "diligent nurse." The attending physicians were skeptical, but recorded and repeated facts spoke for themselves.

The importance of accurate and inquisitive observation is, unfortunately, too often overlooked. This applies not only to the bedside but also to the laboratory. The halo of absent colonies about the growth of mold which Drummond saw on the Petri dish was not unique but the inquisitive mind was.

Elaborate apparatus and complicated biochemical reactions cannot entirely supplant keen clinical observations.

J.C.M.

Book Reviews

DIGITALIS AND OTHER CARDIOTONIC DRUGS. Second Edition, revised and enlarged. By Eli Rodin Movitt, M.D., Chief of Medicine, Veterans' Administration Hospital, Oakland, California; Diplomate of the American Board of Internal Medicine; Major, Medical Corps, Army of the United States (Inactive). New York, 1949, Oxford University Press, 245 pages and 20 figures. Price $5.75.

In this edition, the author follows the same general plan as in the first. Here also he devotes the greater part of the text to a consideration of digitalis and its glycosides. In these sections he considers more extensively the action of digitalis upon venous pressure and, as a consequence, its effect on peripheral blood flow. It therefore follows that when the author deals with congestive heart failure, he gives more consideration to the newer aspects of the role of the peripheral circulation in this complex pathological disturbance. He gives a brief and balanced account of the different schools of thought. Although the indications for digitalis therapy have gone through many cycles since the days of Withering, there are still gaps in our knowledge of the action of this drug. It is true that there is a fair unanimity of opinion as to what it may do under certain circumstances but how this is accomplished remains a matter of debate as to whether it acts primarily upon the myocardium or upon the conduction system, and in the latter case, whether it be a direct effect or through the vagus nerves. This is reminiscent of 1900. That digitalis has a multiplicity of physiological effects seems beyond doubt.

It is generally conceded that it does have an influence upon myocardial contraction, but how this action is brought about remains to be included in our clinical pharmacology. There is, however, an increasing volume of experimental data which, it is hoped, will soon find practical expression.

J.C.M.

THE DIAGNOSIS AND TREATMENT OF ADRENAL INSUFFICIENCY. By George W. Thorn, M.D., Hersey Professor of the Theory and Practice of Physic, Harvard Medical School; and Physician-in-Chief, Peter Bent Brigham Hospital, Boston, Mass. With the collaboration of Peter H. Forsham, M.D., M.A. (Cantab.), Assistant in Medicine, Harvard Medical School and Peter Bent Brigham Hospital, Boston, Mass., and Kendall Emerson, Jr., M.D., Associate in Medicine, Harvard Medical School, and Senior Associate in Medicine, Peter Bent Brigham Hospital, Boston, Mass. Springfield, Ill., 1949, Charles C Thomas, publisher, 171 pages. Price $5.50.

In this monograph, the author has given to the profession an epitome of the diagnosis and treatment of adrenal insufficiency. It is most opportune that this has been done and fitting that it should be at this time as it is a little over one hundred years ago since Thomas Addition described one of the clinicopathological syndromes which bears his name.

The author has briefly outlined the types of adrenal cortical insufficiency from the most acute to the chronic. The signs and symptoms, and the laboratory findings of Addison's Disease are clearly described. An important section is that entitled, "Screening and Tolerance Tests in Adrenal Cortical Insufficiency." Some of these are not without their dangers and some must be carried out with meticulous care and an appreciation of their interpretation to avoid mistakes of omission and commission. Inherent in the pathological physiology of adrenal disease there is a continuing quantitative variability which is so common in many states of impaired function.

It is under these circumstances that the tolerance tests have their greatest value. Two sections are given to the diagnosis and differential diagnosis of cortical adrenal insufficiency.

Of great value to the practicing physician are those chapters devoted to the treatment of adrenal crises under varying conditions, chronic adrenal cortical insufficiency, both complicated and uncomplicated, and the handling of patients with Addition's disease who are being subjected to surgical interference. Lastly, there is a timely word of warning and guidance in dealing with toxic or undesirable reactions met with in the use of adrenal hormone preparations, and the prognosis of adrenal cortical insufficiency.

J.C.M.

ANGINA PECTORIS AND MYOCARDIAL INFARCTION. By Heymen R. Miller, M.D., formerly Principal Physician and Chief, Signal Corps Climatic Research; Attending Physician, Sydenham Hospital; Assistant Professor of Medicine, New York Postgraduate Medical School and Hospital. Associate Attending Physician, Montefiore Hospital. New York, 1950, Grune and Stratton, Inc., 336 pages. Price $8.75.

The author has given an excellent account of the subjects in the title, namely: angina pectoris and myocardial infarction. He has not wasted a great deal of space upon accounts of their general clinical aspect. Section Two deals with the physiological aspects where he outlines, in considerable detail, the autonomic regulations of the circulation. This is in preparation for Sections Three, Four, and Five, where there is an extensive account of cardiac pain. These three sections in themselves make the volume well worth while for all serious students of these diseases. They are excellently illustrated by clear and not too complicated drawings which are a great assistance in the visualization of the pain pathways and reflex and referred stimuli.

The general management and medical treatment are adequately covered, but without the understanding laid down in the sections on cardiac and anginal pain it would be difficult to appreciate the fundamentals of the neurological and paravertebral block therapy.

The references of each section are thorough, and they are made more valuable by an author- and subject-index. The format is pleasing and the typography excellent.

J.C.M.

Notice

It has been recently announced that the papers presented at the First International Cardiovascular Congress, which is being held in Paris from September 3 to 9, 1950, will be published in the *Archives des maladies du coeur*.

Information has also been received that The International Society for Internal Medicine will hold its first formal meeting in Paris immediately following that of the Congress. The program of the Society is being prepared under the direction of Professor A. Gigon, 1, Hebelstrasse, Basle, Switzerland, and Professor Svartz, Karolinski Sjukhuset, Stockholm 60, Sweden.

American Society for the Study of Arteriosclerosis

The Annual Meeting of the Society will be held at the Knickerbocker Hotel, Chicago, November 5 and 6, 1950. Contributions to the scientific program are invited. Titles and abstracts (not exceeding 200 words) should be sent not later than June 15, 1950, to Dr. G. Lyman Duff, Chairman of the Program Committee, 3775 University Street, Montreal, Canada.

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